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(57) Abstract

The present invention provides compositions and methods for the treatment of HIV infection. In particular, the present invention provides non-nucleoside inhibitors of reverse transcriptase (RT), as well as methods to treat HIV infection using these non-nucleoside inhibitors of RT. In preferred embodiments, the present invention provides a novel class of substituted benzimidazoles, effective in the inhibition of human immunodeficiency virus (HIV) RT.

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SUBSTITUTED BENZIMIDAZOLES AS NON-NUCLEOSIDE INHIBITORS OF REVERSE TRANSCRIPTASE

The present application claims priority benefit of U.S. provisional application No. 60/038.509. filed February 25. 1997, pending. which is hereby incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention is related to non-nucleoside inhibitors of reverse transcriptase (RT). In particular, the present invention relates to a novel class of substituted benzimidazoles effective in the inhibition of human immunodeficiency virus (HIV) RT.

BACKGROUND OF THE INVENTION

Since its recognition in 1981, the acquired immunodeficiency syndrome (AIDS) has become a major pandemic. The worldwide prevalence of HIV infection has been estimated at more than 18,500,000 cases, with an additional estimate of 1.5 million infected children (R. Famighetti, *1996 World Almanac and Book of Facts*, World Almanac Books. Mahwah. New Jersey, [1995], p. 840).

The etiologic agent associated with AIDS was identified as the human immunodeficiency virus (HIV). HIV is classified as a retrovirus, as it contains reverse transcriptase (RT), a multi-functional enzyme that contains RNA-dependent DNA polymerase activity, as well as DNA-dependent DNA polymerase and ribonuclease H activities. These three activities are essential for the conversion of genomic retroviral RNA into double-stranded DNA that can then be integrated into an infected host cell genome.

HIV is a D-type virus within the lentivirus family, with two major antigenic types (HIV-1 and HIV-2). HIV-1 and HIV-2 share approximately 40% genetic identity, although they can be readily distinguished based on differences in antibody reactivity to the envelope glycoprotein (M. Cloyd, "Human Retroviruses," *in* S. Baron (ed.), *Medical Microbiology*, University of Texas Medical Branch at Galveston, [1996], pp. 761-775). Both HIV-1 and HIV-2 have been associated with AIDS.

The search for effective drugs against HIV has focused on targeting various critical components of the replication cycle of HIV-1. One important component in this cycle is the reverse transcriptase enzyme. Indeed, perhaps because of its pivotal role in the life cycle of HIV, it was the target of the first clinically approved anti-retroviral agents (*see*. Patel *et al.*. "Insights into DNA Polymerization Mechanisms from Structure and Function Analysis of

HIV-1 Reverse Transcriptase." *Biochem.*. 34:5351-5363 [1995]). although other compounds such as protease inhibitors have recently been introduced. In addition to its critical role in HIV replication. targeting RT has a potential benefit in reducing the toxicity to the patient associated with many drugs, as human cells do not normally contain this RT activity. Therefore. the potential for targeted inhibition of only viral replication, and not host cell multiplication is present. However. this potential has yet to be realized.

There are two major classes of RT inhibitors. The first comprises nucleoside analogues. such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-didehydro-2',3'-dideoxythymidine (d4T), and 2',3'-dideoxycytidine (ddC). These compounds are analogs of normal deoxynucleoside triphosphates (dNTPs). However, these are not specific for HIV RT, and are incorporated into cellular DNA by host DNA polymerases, and can cause serious side effects. Moreover. administration of these analogs has resulted in the emergence of drug-resistant viral strains that contain mutations in their RT. Thus, these RT inhibitors have dangers that must be considered in developing treatment regimens for HIV-infected patients.

The second major class of RT inhibitors comprises the non-nucleoside RT inhibitors (NNRTI). such as tetrahydroimidazo(4,5,1-1-*jk*)(1,4)-benzodiazepin-2-(1*H*)-one, and -thione (TIBO) derivatives. dipyridodiazepinones, pyridinones, bis(heteroaryl)piperazines (BHAPs), 2',5'-bis-O-(tertbutyldimethylsilyl)-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide)pyrimidine (TSAO) derivatives, α -anilinophenylacetamide (α -APA), 8-chloro-4,5,6,7-tetrahydro-5-methylimidazo-[4,5,1-jk][1,4]benzodiazepine-2 (1H)-one (8-Cl TIBO), and nevirapine. (*See*, *e.g.*, Pauwels *et al.*, "Potent and Selective Inhibition of HIV-1 Replication *in Vitro* By a Novel Series of TIBO Derivatives," *Nature* 343:470-474 [1990]; Merluzzi *et al.*. "Inhibition of HIV-1 Replication by a Non-Nucleoside Reverse Transcriptase Inhibitor," *Science* 250:1411-1413 [1990]; Goldman and Stern, "Pyridinone Derivatives: Specific Human Immunodeficiency Virus Type 1 Reverse Transcriptase Inhibitors with Antiviral Activity," *Proc. Natl. Acad. Sci. USA* 88:6863-6867 [1991]; Romero and Tarpley, "Non-Nucleoside Reverse Transcriptase Inhibitors that Potently and Specifically Block Human Immunodeficiency Virus Type 1 Replication," *Proc. Natl. Acad. Sci., USA* 88:8806-8810 [1991]; Balzarini *et al.*, "2',3'-Bis-O-(Tertbutyldimethylsilyl)-3'-Spiro-5''-(4''-Amino-1''.2''-Oxathiole-2'',2''-Dioxide) Pyrimidine (TSAO) Nucleoside Analogs: Highly Selective Inhibitors of Human Immunodeficiency Virus Type 1 That are Targeted at the Viral Reverse Transcriptase," *Proc. Natl. Acad. Sci. USA* 89:4392-4396 [1992]; Young, "Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase." *Perspect. Drug Discov. Des.*. 1:181-192; and

Pauwels *et al.*, "Potent and Highly Selective Human Immunodeficiency Virus Type 1 (HIV-1) Inhibition by a Series of α -Anilinophenylacetamide Derivatives Targeted at HIV-1 Reverse Transcriptase," *Proc. Natl. Acad. Sci., USA* 90:1711-1715 [1993]).

Unlike the nucleoside analogues, the NNRTIs do not act as chain terminators and do not bind at the dNTP-binding site. The majority of these compounds have been shown to share a common binding site unique to HIV-1 RT that is located in proximity to the RT polymerase active site. (*See*, Tantillo *et al.*, "Locations of Anti-AIDS Drug Binding Sites and Resistance Mutations in Three-Dimensional Structure of HIV-1 Reverse Transcriptase. Implications for Mechanisms of Drug Inhibition and Resistance," *J. Mol. Biol.*, 243:369-387 [1994]; Smith *et al.*, "Molecular Modeling Studies of HIV-1 Reverse Transcriptase Nonnucleoside Inhibitors: Total Energy of Complexation as a Predictor of Drug Placement and Activity," *Prot. Sci.*, 4:2203-2222 [1995]; Ding *et al.*, "Structure of HIV-1 TR/TIBO R86183 Complex Reveals Remarkable Similarity in the Binding of Diverse Nonnucleoside Inhibitors." *Nature Struct. Biol.*, 2:407-415 [1995]; and Nanni *et al.*, "Review of HIV-1 Reverse Transcriptase Three Dimensional Structure: Implications for Drug Design," *Perspect. Drug Discov. Des.*, 1:129-150 [1993]).

NNRTIs are highly specific for HIV-1 RT, and do not inhibit either HIV-2 RT or normal cellular polymerases, resulting in lower cytotoxicity and fewer side effects than the nucleoside analogs. (*See*, *e.g.*, Ding *et al.*, "Structure of HIV-1 Reverse Transcriptase in a Complex with the Non-Nucleoside Inhibitor α-APA R 95845 at 2.8 Å Resolution." *Structure* 3:365-379 [1995]). However, resistance to some of these compounds has been reported. (*See*, *e.g.*, Nunberg *et al.*, "Viral Resistance to Human Immunodeficiency Virus Type 1-Specific Pyridinone Reverse Transcriptase Inhibitors," *J. Virol.*, 65:4887-4892 [1991]; Tantillo *et al.*, "Locations of Anti-AIDS Drug Binding Sites and Resistance Mutations in the Three-Dimensional Structure of HIV-1 Reverse Transcriptase: Implications for Mechanisms of Drug Inhibition and Resistance," *J. Mol. Biol.*, 243:369-387; and Richman. "Resistance of Clinical Isolates of Human Immunodeficiency Virus to Antiretroviral Agents," *Antimicrob. Agents Chemother.*, 37:1207-1213 [1993]).

Despite recent developments in drug and compound design to combat HIV, there remains a need for a potent, non-toxic compound that is effective against wild type (WT) RTs, as well as RTs that have undergone mutations, and thereby become refractory to commonly used anti-HIV compounds.

SUMMARY OF THE INVENTION

The present invention is related to substituted benzimidazole compounds. In particular. the present invention provides non-nucleoside inhibitors of reverse transcriptase (RT) comprising a novel class of substituted benzimidazoles effective in the inhibition of human immunodeficiency virus (HIV) RT.

In one embodiment, the present invention provides 1-aryl-2-(2,6-difluorophenyl)benzimidazole compositions with general structure of Figure 12. In particularly preferred embodiments, X" is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl. nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine. In other preferred embodiments, R" is selected from the group consisting of 2.6-difluorobenzyl (2,6-F_2Bn), benzyl (Bn), ethylbenzyl, 2,6-dichlorobenzyl (2,6-Cl_2Bn), 2,3,4,5,6-pentafluorobenzyl (2,3,4,5,6-F_5Bn), pyridylmethyl (CH_2(3-Py), benzenesulfonyl ($PhSO_2$), 2.6-difluorobenzoyl (2,6-F_2Bz), and 3,3-dimethylallyl. In other preferred embodiments, X" is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine; and R" is selected from the group consisting of 2,6-difluorobenzyl, benzyl, ethylbenzyl, 2,6-dichlorobenzyl, 2,3,4,5,6-pentafluorobenzyl, pyridylmethyl, benzenesulfonyl, 2,6-difluorobenzoyl, and 3,3-dimethylallyl. In other preferred embodiments, X" is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine; and R" is 2,6-difluorobenzyl. In yet other preferred embodiments, X" is selected from the group consisting of methoxyl and acetamide, and R" is 2,6-difluorobenzyl.

In an alternative embodiment, the present invention provides 1-(2,6-difluorophenyl)benzimidazole compositions with the general structure of Figure 13. In preferred embodiments, X' is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine. In other preferred embodiments, R' is selected from the group consisting of phenyl (Ph), formyl (CHO), isopropyl (iPr), H, methyl (CH_3), cyclopropyl, hydroxymethyl (CH_2OH), and 2,6-difluorobenzyloxymethyl (CH_2O(2,6-F_2Bn), 2,6 diflourophenyl (2,6-F_2Ph), methylphenyl (2-CH_3Ph), 2-fluoro-6-methoxylphenyl, pyridyl (*e.g.*, 4-Py, 3-Py), and naphthyl (*e.g.*, 1-Nap, 2-Nap). In other preferred embodiments, X' is selected from the group consisting of H and methyl, H, methyl, ethyl, cyano. methoxyl, nitro, amine. acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and

chlorine: and R' is selected from the group consisting of phenyl, formyl, isopropyl, H, methyl, cyclopropyl, hydroxymethyl, 2,6-difluorobenzyloxymethyl, 2,6 diflourophenyl (2,6-F_2Ph), methylphenyl (2-CH_3Ph), 2-fluoro-6-methyoxylphenyl, pyridyl (*e.g.*, 4-Py, 3-Py), and naphthyl (*e.g.*, 1-Nap, 2-Nap). In other preferred embodiments, X' is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine; and R' is 2,6-difluorophenyl. In yet other preferred embodiments, X' is selected from the group consisting of methoxyl and acetamide, and R' is 2,6-difluorophenyl.

In another alternative embodiment, the present invention provides 4-, 5-, 6-, or 7-substituted-1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole compositions of the general structure of Figure 23, wherein X'''' is selected from the group consisting of H, methyl (CH_3), 4-methyl (4-CH_3), 5-methyl (5-CH_3), 6-methyl (6-CH_3), 7-methyl (7-CH_3), 4,5-dimethyl (4,5-CH_3), 4,6-dimethyl (4,6-CH_3), 4-chloro (4-Cl), 5-chloro (5-Cl), 6-chloro (6-Cl), 4-bromo (4-Br), 5-bromo (5-Br), 4-nitro (4-NO_2), and 5-nitro (5-NO_2).

In yet another embodiment, the present invention provides 4-substituted-1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole compositions of the general structure of Figure 24, wherein X''' is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine.

It is contemplated that the substituted benzimidazoles of the present invention comprise derivatives containing various groups. It is not intended that the present invention be limited to particular substituted benzimidazole derivatives. For example, it is intended that the present invention encompasses embodiments in which such groups as aromatic rings, hydrocarbons, and other structures are included. Such groups include, but are not limited to, H, 4-methyl, 5-methyl, 6-methyl, 7-methyl, 4,5-dimethyl, 4,6-dimethyl, 4-chloro, 5-chloro, 6-chloro, 4-bromo, 5-bromo, 4-nitro, and 5-nitro, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, phenyl, formyl, isopropyl, cyclopropyl, hydroxymethyl, 2,6-difluorobenzyloxymethyl, 2,6-diflourophenyl, 2-fluoro-6-methyoxylphenyl, pyridyl, naphthyl, 2,6-difluorobenzyl, benzyl, ethylbenzyl, 2,6-dichlorobenzyl, 2,3,4,5,6-pentafluorobenzyl, pyridylmethyl, benzenesulfonyl, 2,6-difluorobenzoyl, and 3,3-dimethylallyl. It is further intended that these groups be included in these compositions alone or in combination.

It is also contemplated that the aromatic residues of various embodiments of the present invention may be replaced with hydrophobic residues, such as aliphatic groups. For example, the present invention encompasses alkylimidazoles, including, but not limited to 1-(2,6-difluorobenzyl)-2-difluorophenyl-5,6-dialkylimidazole.

It is further contemplated that the present invention includes embodiments in which the carbons (C) present on the benzyl ring (*i.e.*, C-4, C-5, C-6, and C-7) are replaced with nitrogen (N), singly, or in combination (*e.g.*, azapurines).

It is contemplated that the substituted benzimidazoles of the present invention will find use in treatment of HIV infection/disease. In particularly preferred embodiments, the present invention provides compositions of substituted benzimidazoles with activity against HIV-1 RT.

The present invention also provides methods for treatment of human immunodeficiency virus (HIV) infection, comprising the steps of: providing: i) a subject suspected of being infected with human immunodeficiency virus; and ii) a composition having anti-reverse transcriptase activity, wherein the composition comprises at least one substituted benzimidazole with at least one substitution at the C-2 site, and at least one substitution at the N-1 site; exposing the subject to the composition; and observing for inhibition of anti-reverse transcriptase activity. In one preferred embodiment, the human immunodeficiency virus is HIV-1.

In one embodiment, the method for treatment of HIV infection utilized substituted benzimidazoles with the general structure of Figure 12. In particularly preferred embodiments, X" is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine. In other preferred embodiments, R" is selected from the group consisting of 2,6-difluorobenzyl, benzyl, ethylbenzyl, 2,6-dichlorobenzyl, 2,3,4,5,6-pentafluorobenzyl, pyridylmethyl, benzenesulfonyl, 2,6-difluorobenzoyl, and 3,3-dimethylallyl. In other preferred embodiments, X" is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine; and R" is selected from the group consisting of 2,6-difluorobenzyl, benzyl, ethylbenzyl, 2,6-dichlorobenzyl, 2,3,4,5,6-pentafluorobenzyl, pyridylmethyl, benzenesulfonyl, 2,6-difluorobenzoyl, and 3,3-dimethylallyl. In other preferred embodiments, X" is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine; and R" is 2,6-

difluorobenzyl. In yet other preferred embodiments, X" is selected from the group consisting of methoxyl and acetamide, and R" is 2,6-difluorobenzyl.

In an alternative embodiment, the method for treatment of HIV infection utilized substituted benzimidazoles with the general structure of Figure 13. In particularly preferred embodiments, X' is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine. In other preferred embodiments, R' is selected from the group consisting of phenyl (Ph), formyl (CHO), isopropyl (iPr), H, methyl (CH_3), cyclopropyl, hydroxymethyl (CH_2OH), and 2,6-difluorobenzyloxymethyl (CH_2O(2,6-F_2Bn), 2,6 diflourophenyl (2,6-F_2Ph), methylphenyl (2-CH_3Ph), 2-fluoro-6-methoxylphenyl, pyridyl (*e.g.*, 4-Py, 3-Py), and naphthyl (*e.g.*, 1-Nap, 2-Nap). In other preferred embodiments, X' is selected from the group consisting of H and methyl, H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine; and R' is selected from the group consisting of phenyl, formyl, isopropyl, H, methyl, cyclopropyl, hydroxymethyl, 2,6-difluorobenzyloxymethyl, 2,6 diflourophenyl (2,6-F_2Ph), methylphenyl (2-CH_3Ph), 2-fluoro-6-methyoxylphenyl, pyridyl (*e.g.*, 4-Py, 3-Py), and naphthyl (*e.g.*, 1-Nap, 2-Nap). In other preferred embodiments, X' is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine; and R' is 2,6-difluorophenyl. In yet other preferred embodiments, X' is selected from the group consisting of methoxyl and acetamide, and R' is 2,6-difluorophenyl.

In another alternative embodiment, the method for treatment of HIV infection utilized substituted benzimidazoles with the general structure of Figure 23. In particularly preferred embodiments, X'''' is selected from the group consisting of H, methyl (CH_3), 4-methyl (4-CH_3), 5-methyl (5-CH_3), 6-methyl (6-CH_3), 7-methyl (7-CH_3), 4,5-dimethyl (4,5-CH_3), 4,6-dimethyl (4,6-CH_3), 4-chloro (4-Cl), 5-chloro (5-Cl), 6-chloro (6-Cl), 4-bromo (4-Br), 5-bromo (5-Br), 4-nitro (4-NO_2), and 5-nitro (5-NO_2).

In yet another alternative embodiment, the method for treatment of HIV infection utilized substituted benzimidazoles with the general structure of Figure 24. In particularly preferred embodiments, X''' is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine.

In addition, it is contemplated that the present invention encompasses analogs of the benzimidazole ring system which undergo dissociation in the binding pocket of HIV RT, to give rise to electrophilic intermediates that react with nucleophilic sites in the pocket. Thus, it is contemplated that compounds that act as irreversible inhibitors of HIV RT also be encompassed as embodiments within the present invention.

It is not intended that the compounds of the present invention be limited to any particular use. Indeed, it is intended that the compounds of the present invention will be utilized against organisms other than HIV.

DESCRIPTION OF THE FIGURES

Figure 1 shows the general structures of imidazole and benzimidazole.

Figure 2 is a schematic of the retrosynthetic analysis of *N*-benzyl-2-alkylbenzimidazoles by alkylation of 2-substituted benzimidazoles.

Figure 3 shows one embodiment for the synthesis of 2-aryl-benzimidazoles.

Figure 4 shows one embodiment for the synthesis of hydroxymethyl substituted benzimidazole.

Figure 5 shows the structure, as well as physical and biological data for 1-(2,6-difluorobenzyl)-2-aryl-benzimidazoles.

Figure 6 shows the structure, as well as physical and biological data for 1-aryl-2-(2,6-difluorophenyl)-benzimidazoles.

Figure 7 shows the structure, as well as physical and biological data for 1-(2,6-difluorobenzyl)-2-substituted-benzimidazoles.

Figure 8 shows the anti-RT activity of compounds **33** and **26**, compared with TZB and TIBO. Antiviral data are reported as the quantity of drug in μM required to reduce cell killing or virus production by 50% (EC_{50}).

Figure 9 shows the "butterfly-like" shape of TZB and **39**.

Figure 10 shows the structure of four compounds that did not inhibit RT activity.

Figure 11 shows the substitutions of the benzimidazole core ring that inhibited as well as substitutions that did not inhibit HIV RT.

Figure 12 shows the structure of 1-aryl-2-(2,6-difluorophenyl)benzimidazole.

Figure 13 shows the structure of 1-(2,6-difluorobenzyl)-2-benzimidazole.

Figure 14 shows one embodiment for the synthesis of substituted 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazoles.

Figure 15 shows one embodiment for the reduction of the 4-nitro group of **3100** with tin chloride.

Figure 16 shows the structure, physical, and enzyme inhibition data for 4-, 5-, 6- and 7-methyl-substituted 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-benzimidazoles.

Figure 17 shows the structure, physical, and enzyme inhibition data for 4-, 5-, and 6-substituted 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazoles (Cl, Br, NO_2).

Figure 18 shows the structure, physical, and enzyme inhibition data for 4- substituted 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazoles.

Figure 19 shows the anti-RT activity of CH_3, NH_2, Cl, Br-substituted compounds, compared with TZB and TIBO. Antiviral data are reported as the quantity of drug in μM required to reduce cell killing or virus production by 50% (EC_{50}).

Figure 20 is a summary graph showing the cytotoxicity and anti-viral effect of compound **33**.

Figure 21 is a summary graph showing the cytotoxicity and anti-viral effect of compound **34**.

Figure 22 is a summary graph showing the anti-viral results for inactive compound **2100**.

Figure 23 shows the structure of 5,6, or 7-substituted-1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole.

Figure 24 shows the structure of 4-substituted 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole.

Figure 25 shows the calculated and actual purities of various substituted 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazoles.

Figure 26 shows one embodiment for the synthesis of 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-cyanobenzimidazole.

Figure 27 shows one embodiment for the synthesis of *N*-substituted-2-(2,6-difluorophenyl)-4-methoxylbenzimidazole.

Figure 28 shows one embodiment for the syntheses of *N*-substituted-(2,6-difluorophenyl)-4-methylbenzimidazoles and *N*-substituted-(2,6-difluorophenyl)-4-ethylbenzimidazoles.

Figure 29 shows one embodiment for the synthesis of substituted 1-(2,6-difluorobenzyl)-2-arylbenzimidazoles.

Figure 30 shows one embodiment for the synthesis of *N*-substituted-2-(cyclopropyl)-4-methoxylbenzimidazole.

Figure 31 shows one embodiment of the synthesis of 4-substituted *N*-substituted-2-(2,6-difluorophenyl)benzimidazoles.

Figure 32 shows the cross resistance profile of 4-Substituted 1-(2,6-difluorobenzoyl)-2-(2,6-difluorophenyl)benzimidazoles in a cytopathic cell killing assay. Antiviral data are reported as the quantity of drug in μM required to reduce cell killing or virus production by 50% (EC_{50}).

DESCRIPTION OF THE INVENTION

The present invention provides substituted benzimidazole compounds, which act as non-nucleoside inhibitors of reverse transcriptase (RT). In particular, the present invention relates to a novel class of substituted benzimidazoles, effective in the inhibition of human immunodeficiency virus (HIV) RT.

Definitions

To facilitate understanding of the invention, a number of terms are defined below.

As used herein, the term "retrovirus" refers to the group of viruses with RNA genomes. Retroviruses are characterized as having reverse transcriptase, the enzyme that allows the RNA genome to be transcribed into DNA.

As used herein, the term "reverse transcriptase" refers to an enzyme with RNA-dependent DNA polymerase activity, with or without the usually associated DNA-dependent DNA polymerase and ribonuclease activity observed with wild-type reverse transcriptases.

As used herein, the term "anti-viral" is used in reference to any compound, substance, or molecule capable of inhibiting or preventing viral replication and/or dissemination. It is intended that the term encompasses compounds capable of inhibiting viral replication by interfering with such activities as the reverse transcriptase activity of retroviruses. It is also intended to encompass "non-nucleoside reverse transcriptase inhibitors" (NNRTI). In preferred embodiments, the term is used in reference to substituted benzimidazole compounds.

As used herein, the term "chemotherapeutic" refers to any compound, element, or substance useful against disease. In preferred embodiments, the term encompasses compounds such as the substituted benzimidazoles of the present invention.

As used herein, the term "purified" refers to the removal of contaminants from a sample. Methods such as carbon, hydrogen and nitrogen analyses (CHN analysis. or "elemental analysis") may be used to determine the purity of compounds. In preferred embodiments. the CHN values of compounds of the present invention are very close to the predicted values. Correspondence of experimental with the predicted values to within 0.3% indicates high levels of purity. In particularly preferred embodiments, the compounds of the present invention have CHN values within 0.3% of the predicted values. In less preferred embodiments, the level of purity may be lower (*i.e.*, greater than 0.3% difference between the predicted and actual CHN values).

As used herein, the term "benzimidazole" is used in reference to molecules with the core structure as indicated in Figure 1. It is intended that the term encompasses compounds in which substitutions. including additions, have been made to the chemical structure. The term encompasses, but is not limited to substitution reactions, wherein there is replacement of one or more atom or group in a molecule by another atom or group.

As used herein, the term "TZB" refers to 1-(2,6-difluorophenyl)-1H,3-thiazolo[3,4-α]benzimidazole. In preferred embodiments, the present invention encompasses 1,2-substituted benzimidazoles, including but not limited to 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-methylbenzimidazole.

The term "cyclic compounds" refers to compounds having one (*i.e.*, a monocyclic compounds) or more than one (*i.e.*, polycyclic compounds) ring of atoms. The term is not limited to compounds with rings containing a particular number of atoms. While most cyclic compounds contain rings with five or six atoms, rings with other numbers of atoms (*e.g.*, three or four atoms) are also contemplated by the present invention. The identity of the atoms in the rings is not limited, though the atoms are usually predominantly carbon atoms. Generally speaking, the rings of polycyclic compounds are adjacent to one another; however, the term "polycyclic" compound includes those compounds containing multiple rings that are not adjacent to each other.

The term "heterocyclic compounds" refers broadly to cyclic compounds wherein one or more of the rings contains more than one type of atom. In general, carbon represents the predominant atom, while the other atoms include, for example, nitrogen, sulfur, and oxygen. Examples of heterocyclic compounds include benzimidazole, furan, pyrrole, thiophene, and pyridine.

The terms "aromatic," "aromatic compounds," and the like refer broadly to compounds with rings of atoms having delocalized electrons. The monocyclic compound benzene (C_6H_6) is a common aromatic compound. However, electron delocalization can occur over more than one adjacent ring (*e.g.*, naphthalene [two rings] and anthracene [three rings]). Different classes of aromatic compounds include, but are not limited to, aromatic halides (aryl halides), aromatic heterocyclic compounds, aromatic hydrocarbons (arenes), and aromatic nitro compounds (aryl nitro compounds).

As used herein, the terms "aliphatic" and "aliphatic compounds" refer to compounds which comprise carbon atoms in chains, rather than the ring structure of aromatic compounds. It is intended that these aliphatic moieties will be bound to additional elements in some embodiments.

The terms "resistant" and "refractory" used in reference to "resistant mutants" of HIV and/or HIV RT, refer to the ability of some HIV RTs to function in the presence of compounds that are inhibitory to the RT of wild-type HIV. This resistance may result from any number of mutations, including but not limited to conformational changes in the RT structure, as well as the configuration of the RT bound to its substrate.

The term "mixture" refers to a mingling together of two or more substances without the occurrence of a reaction by which they would lose their individual properties. The term "solution" refers to a liquid mixture. The term "aqueous solution" refers to a solution that contains some water. In many instances, water serves as the diluent for solid substances to create a solution containing those substances. In other instances, solid substances are merely carried in the aqueous solution (*i.e.*, they are not dissolved therein). The term aqueous solution also refers to the combination of one or more other liquid substances with water to form a multi-component solution.

The terms "sample" and "specimen" in the present specification and claims are used in their broadest sense. On the one hand, they are meant to include a specimen or culture. On the other hand, they are meant to include both biological and environmental samples. These terms encompass all types of samples obtained from humans and other animals, including but not limited to, body fluids such as urine, blood, fecal matter, cerebrospinal fluid (CSF), semen, and saliva, as well as solid tissue. These terms also refer to swabs and other sampling devices which are commonly used to obtain samples for culture of microorganisms.

Biological samples may be animal, including human, fluid or tissue, food products and ingredients such as dairy items, vegetables, meat and meat by-products, and waste.

Environmental samples include environmental material such as surface matter, soil, water, and industrial samples, as well as samples obtained from food and dairy processing instruments, apparatus, equipment, disposable, and non-disposable items. These examples are not to be construed as limiting the sample types applicable to the present invention.

As used herein, the term "culture" refers to any sample or specimen which is suspected of containing one or more microorganisms. "Pure cultures" are cultures in which the organisms present are only of one strain of a particular genus and species. This is in contrast to "mixed cultures," which are cultures in which more than one genus, species, and/or strain of microorganism are present.

As used herein, the term "organism" is used to refer to any species or type of microorganism, including but not limited to viruses. In particular, the term is used in reference to RNA viruses, such as the retroviruses. In preferred embodiments, the organism of interest is HIV. In particularly preferred embodiments, the organism of interest is HIV-1.

The term "parenterally" refers to administration to a subject through some means other than through the gastrointestinal tract or the lungs. The most common mode of parenteral administration is intravenous. However, other modes of parenteral administration include, but are not limited to, intramuscular, and subcutaneous administration.

The phrase "pharmaceutical preparation suitable for parenteral administration" refers to a solution containing compound in a pharmaceutically acceptable form for parenteral administration. The characteristics of the form will depend on a number of factors, including the mode of administration. For example, a preparation for intravenous administration will often comprise compound dissolved in normal saline or sterile water for injection. Of course, the pharmaceutical preparations of the present invention are not limited to those diluents; indeed, other components or diluents known in the field of pharmaceuticals and pharmacy are within the scope of the present invention. The pharmaceutical preparation may contain diluents, adjuvants and excipients, among other components, provided that those additional components neither adversely effect the preparation (*e.g.*, they do not cause degradation of the compound) nor the recipient (*e.g.*, they do not cause a hypersensitivity reaction).

Imidizoles And Benzimidazoles

In addition to compounds such as tetrahydroimidazo(4,5,1-1-*jk*)(1,4)-benzodiazepin-2-(1*H*)-one, and -thione (TIBO) derivatives, dipyridodiazepinones, pyridinones, bis(heteroaryl)piperazines (BHAPs), 2',5'-bis-O-(tertbutyldimethylsilyl)-3'-spiro-5''-(4''-

amino-1''.2''-oxathiole-2''.2''-dioxide)pyrimidine (TSAO) derivatives, α-anilinophenylacetamide (α -APA), 4,5,6,7-tetrahydro-5-methylimidazo-[4,5,1-jk][1,4]benzodiazepine-2 (1H)-one (TIBO), and nevirapine, the potential therapeutic utility of imidazole compounds such as 1-(2,6-difluorophenyl)-1H,3H-thiazolo[3,4-α]benzimidazole (TZB) has been shown. (*See, e.g.*, A. Chimirri *et al.*, "Anti-HIV Agents: Synthesis and In Vitro Anti-HIV Evaluation of Novel 1H,3H-Thiazolo[3,4-α]Benzimidazoles," *Il Farmaco* 46:817-823 [1991]).

As shown in Figure 1, imidazoles (*i.e.*, glyoxaline, 1,2-diazole, iminazole, miazole, pyrro[*b*]monazole, and 1,3-diaza-2,4-cyclopentadiene), are five-membered heterocycles with the formula $C_3H_4N_2$. The properties of these compounds permit the existence of cyclic aromatic structures (*i.e.*, derivatives) with more than two nitrogens or other heteroatoms bonded together. Many derivatives of these heterocyclic structures are important biochemical intermediates. Figure 1 also shows the structure of benzimidazole (*i.e.*, benziminazole, 1,3-benzodiazole, azindole, benzoglyoxaline, *N,N'*-methenyl-*o*-phenylenediamine, with the formula $C_7H_6N_2$). The numbering conventions for the ring positions are indicated in these structures.

Imidazoles (*e.g.*, clotrimazole, miconazole, econazole, and isoconazole) have found clinical use as anti-fungals, as they inhibit fungal cell ergosterol synthesis, but do not readily interfere with cholesterol synthesis in host (*e.g.*, mammalian) cells. However, these drugs have undesirable side effects when administered systemically, such as pruritis, anemia, hyponatremia, leukopenia, thrombocytopenia, and elevated liver enzymes. Thus, their use has mainly been limited to topical treatment of fungal infections. Ketoconazole (another imidazole) is water-soluble and is easily absorbed from the gastrointestinal tract for oral treatment of systemic fungal infections. Although good results are usually obtained with otherwise healthy patients, severe problems in immunocompromised patients have been reported.

Benzimidazoles (*e.g.*, thiabendazole, mebendazole, and albendazole) have found clinical use as anti-helmintics, as they are effective against both the larval and adult stages of nematodes that cause ascariasis, intestinal capillariasis, enterobiasis, trichuriasis, as well as single and mixed hookworm infection. However, as with the imidazoles, the toxicity of these compounds, and/or their limited bioavailability has limited their clinical utility.

Benzimidazole derivatives have been investigated as anti-viral agents, and some have been recognized as being capable of inhibiting RNA viruses. (*See, e.g.*, Gilbert *et al.*, *Antiviral Res.*, 9:355 [1988]). In addition, it has been recognized that thiazolobenzimidazole

analogs may enhance the immune response. (*See*, *e.g.*, Warren *et al.*, *Immunopharmacol.*, 1:269 ([1979]; Fenichel *et al.*, *Immunopharmacol.*, 2:491 [1981]; and U.S. Patent No. 4,214.089 to Fenichel *et al.*, herein incorporated by reference). Other derivatives of thiazolobenzimidazole, such as 1-phenyl substituted 1H,3H-thiazole[3,4-α] benzimidazoles have also been reported as having anti-HIV-1 RT activity. (*See*, *e.g.*, EP 0471991, to Monforte *et al.*).

As mentioned above, one thiazolobenzimidazole compound, TZB, has been shown to have HIV-1 RT inhibitory activity. However, there are some drawbacks to the use of TZB. (*See*, *e.g.*, Chimirri *et al.*, Anti-HIV Agents. I. Synthesis and *In Vitro* Anti-HIV Evaluation of Novel 1H,3H-Thiazolo[3,4-α]Benzimidazoles," *Il Farmaco* 46:817-823 [1991]; Chimirri *et al.*, "Anti-HIV Agents. II. Synthesis and *In Vitro* Anti-HIV Evaluation of Novel 1H,3H-Thiazolo[3,4-1]Benzimidazoles," *Il Farmaco* 46:925-933 [1991]; and Buckheit *et al.*, "Thiazolobenzimidazole: Biological and Biochemical Anti-Retroviral Activity of a New Non-Nucleoside Reverse Transcriptase Inhibitor," *Antiviral Res.*, 21:247-265 [1993]). One problem with TZB is its susceptibility to metabolic oxidation of the thiazolo ring, resulting in the formation of less potent sulfoxide and sulfone metabolites (El Dareer *et al.*, "Metabolism and Disposition of a Thiazolobenzimidazole Active Against Human Immunodeficiency Virus-1," *Drug Metabol. Dispos.*, 21:231-235 [1993]).

Another problem is the loss of antiviral activity against HIV strains with mutated RT. (*See*, Boyer *et al.*, Analysis of Nonnucleoside Drug-Resistant Variants of Human Immunodeficiency Virus Type 1 Reverse Transcriptase," *J. Virol.*, 67:2412-2420; and Buckheit *et al.*, "Comparative Anti-HIV Evaluation of Diverse HIV-1 Specific Reverse Transcriptase Inhibitor-Resistant Virus Isolates Demonstrates the Existence of Distinct Phenotypic Subgroups," *Antiviral Res.*, 26:117-132 [1995]). During the development of the present invention, the drawbacks of TZB were addressed in order to provide NNRTIs capable of efficiently and effectively inhibiting wild type, as well as mutated HIV-1 RT, with low toxicity levels, and a favorable therapeutic dose.

During early stages in the development of the present invention, retrosynthetic analysis was applied to TZB. This indicated that opening the thiazolo ring of TZB could result in the production of compounds potentially useful for inhibition of HIV RT, and resulted in the development of the novel benzimidazoles disclosed herein. Figure 2 shows a schematic for one embodiment of the present invention, in which *N*-benzyl-2-alkylbenzimidazoles are synthesized by alkylation of 2-substituted benzimidazoles, as was attempted during the

development of the present invention. These substituted *N*-benzyl-benzimidazoles were of interest as potentially providing enhanced inhibition of wild type RT, and the various clinically observed variant forms of HIV RT. This was one highly important aspect of the present invention, as most of the known NNRTIs are rendered ineffective by the emergence of mutant forms of HIV. (*See*, De Clercq, "HIV Resistance to Reverse Transcriptase Inhibitors," *Biochem. Pharm.*, 47:155-169 [1994]). Especially in view of the development of resistance to compounds previously effective against HIV, it was of great interest to develop compounds effective against mutants of HIV RT. For example, development of a compound that was effective against Y181 C, a mutant that has a high degree of resistance to most NNRTIs, such as α -APA, nevirapine, and TIBO derivatives was a major consideration in the development of the present invention. (*See, e.g.*, "Structure of HIV-1 RT/TIBO R86183 Complex Reveals Similarity in the Binding of Diverse Nonnucleoside Inhibitors," *Struct. Biol.*, 2:407-415 [1995]). Thus, during the development of the present invention, various compounds were developed and tested for their ability to inhibit both WT and mutated forms of HIV-1 RT. Various approaches were taken in order to produce these compounds, including synthesizing benzimidazoles with substitutions at one or more positions.

Synthesis Of Substituted Benzimidazoles

Figure 3 provides one embodiment of a general outline of the approach for the synthesis of 2-aryl-benzimidazoles. As shown in Figure 3, a variety of 2-aryl-benzimidazoles were made available by use of the appropriate choice of acylating reagent. In most cases, it was found that high yields of the desired *N*-acyl-nitroaniline could be obtained from either 2-nitroaniline (**8**), or 2-methyl-6-nitroaniline (**9**). In this Figure, "a" comprised aroyl chloride, pyridine/THF (tetrahydrofuran); "b" comprised Fe (**17**)/AcOH (iron/acetic acid); "c" comprised 2,6-F_2-BnBr (**25**) (2,6-difluorobenzylbromide)/NaH (sodium hydride)/THF; and "d" comprised BnBr (**27**) (benzyl bromide) or $PhSO_2Cl$ (**44**) (benzenesulfonyl chloride) or 2,6-F_2BzCl (**7**) (2,6-difluorobenzoylchloride)/THF.

Only in the case of 1-naphthyl derivative (**14**) was a mixture of mono and bis acylated product formed. Subsequent reductive cyclization of compounds (**10-16**) with iron yielded the desired 2-aryl-benzimidazoles (**18-24**). Following their coupling with 2,6-difluorophenyl-α-bromotoluene (**25**), the desired 2-aryl-1-(2,6-difluorobenzyl)-benzimidazoles (R_2= 2,6-difluorophenyl [**26** and **33**]; 2-methylphenyl [**36**]; napthyl [**37** and **38**]; pyridyl [**40** and **41**]) were obtained.

The first 2-substituted derivatives of *N*-2(2,6-difluorobenzyl)benzimidazole studied during the development of the present invention were the methyl, hydroxymethyl, isopropyl, carboxyl, formyl, and phenyl derivatives. With methyl and phenyl compounds, commercially available benzimidazoles were reacted with 2,6-difluorophenyl-α-bromotoluene (**25**) to give compounds (**35** and **39**). Preparation of the hydroxymethyl substitute was achieved by acid-catalyzed condensation-cyclization of glycolic acid with either *o*-phenylenediamine (**1**) or 2,3-diaminotoluene (**3**), using an approach similar to that described by Chimirri *et al.* for the synthesis of TZB. (Chimirri *et al.*, Anti-HIV Agents. I. Synthesis and *In Vitro* Anti-HIV Evaluation of Novel 1H,3H-Thiazolo[3,4-α]Benzimidazoles," *Il Farmaco* 46:817-823 [1991]; and Chimirri *et al.*, "Anti-HIV Agents. II. Synthesis and *In Vitro* Anti-HIV Evaluation of Novel 1H,3H-Thiazolo[3,4-1]Benzimidazoles," *Il Farmaco* 46:925-933 [1991]). One embodiment, showing this approach is presented schematically in Figure 4. In this Figure, "a" comprised glycolic or isobutyric acid/4 N HCl (hydrochloric acid)/reflux; "b" comprised 2,6-F_2-BzCl (**7**) or 2,6-F_2BnBr (**25**); "c" comprised *t*-butyldimethylsilylchloride (tBDMSCl)/ pyridine; "d" comprised Bu_4NF (tetrabutylammonium fluoride)/THF; "e" comprised $KMnO_4$ (potassium permanganate); and "f" comprised CrO_3 (chromium trioxide)..

In the embodiment presented in Figure 4, the hydroxymethyl was then protected with *t*-butyldimethylsilyl (TBDMS) before *N*-alkylation with 2,6-difluorophenyl-α-bromotoluene (**25**). Removal of TBDMS from (**31**) resulted in the production of 1-(2,6-difluorobenzyl)-2-hydroxymethyl-4-methylbenzimidazole (**49**).

However, oxidation of the hydroxymethyl to the carboxylic acid was found to be problematic. When a strong oxidant (*e.g.*, $KMnO_4$) was used, the isolated product (**50**) indicated that decarboxylation occurred under acidic reaction conditions. Oxidation under basic conditions with chromium trioxide similarly yielded (**50**), along with the formyl product (**51**). The carboxylic acid form was not isolated. A final product prepared from the 2-hydroxymethylbenzimidazole (**4**) was the bis-2,6-difluorobenzyl derivative (**32**).

A variety of 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole compounds with general structure of Figure 12 were prepared by use of the appropriate choice of acylating reagent. Figure 26 shows the synthesis of 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-cyanobenzimidazole (**4007**). In this Figure, "a" comprised difluorobenzoyl chloride/pyridine/THF; "b" comprised hydrazine/pyridine; "c" comprised iron powder; "d" comprised 2,6-difluoro-α-bromo-toluene; "e" comprised barium hydroxide/AcOH; and "f" comprised 1.0 M solution of $AlMe_2NH_2$ (dimethylaluminum amine)/xylene. Figure 27 shows

the preparation of 2-(2,6-difluorophenyl)-4-methoxylbenzimidazoles with general structure of Figure 12. In this figure, "a" comprised K_2CO_3 (potassium carbonate)/methyl iodide/acetone; "b" comprised difluorobenzoyl chloride/pyridine/THF; "c" comprised hydrazine/pyridine; "d" comprised iron powder; "e" comprised 2,6-difluoro-α-bromo-toluene; "f" comprised benzyl bromide; "g" comprised (1-bromoethyl)benzene; and "h" comprised 3,3-dimethylallyl bromide. Figure 28 shows the preparation of 2-(2,6-difluorophenyl)-4-ethylbenzimidazole and 2-(2,6-difluorophenyl)-4-methylbenzimidazole with general structure of Figure 12. In this figure, "a" comprised difluorobenzoyl chloride; "b" comprised iron powder; "c" comprised 2,6-difluoro-α-bromo-toluene; "d" comprised 3,3-dimethylallyl bromide. Figure 31 shows the preparation of a variety of 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole compounds with general structure of Figure 12. In this figure, "a" comprised 3,3-dimethylallyl bromide; "b" comprised iron powder; and "c" comprised concentrated H_2SO_4 (sulfuric acid).

A variety of 1-(2,6-difluorobenzyl)benzimidazole compositions with general structure of Figure 13 was prepared. Figure 29 shows the preparation of 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-(*N*-substituted)benzimidazole with general structure of Figure 13. In this figure, "a" comprised $SnCl_2x2H_2O$ (tin(II) chloride); "b" comprised methyl iodide/THF/NaH; and "c" comprised HCl. Figure 30 shows the preparation of 1-(2,6-difluorobenzyl)-2-(cyclopropyl)-4-methoxylbenzimidazole (**5016**). In this figure, "a" comprised cyclopropanecarbonyl chloride; "b" comprised iron powder; "c" comprised 3,3-dimethylallyl bromide; and "d" comprised 2,6-difluoro-α-bromo-toluene.

The final series of compounds synthesized as described above, were analyzed in order to determine whether the position and nature of the substituents on the benzyl ring at N-1, were analogous to those in the TZB series. In this series, the optimal anti-HIV activity was achieved when the phenyl ring was substituted at the 2- and 6- position with fluorine. Treatment of benzimidazole (**18** or **19**) with benzyl bromide analogs (benzyl bromide itself, 2,6-dichloro-α-bromo-toluene, 2,3,4,5,6-pentafluoro-α-bromo-toluene), permitted the determination of whether compounds with hydrogen, chlorine, or multiple fluorines on N1 benzyl ring were better inhibitors of HIV-1 RT.

Since a number of NNRTI contain sulfonyl links (*e.g.*, 2-nitrophenyl phenyl sulfone, and 5-chloro-3-(phenylsufonyl)-indole-2-carboxamide), it was also determined whether a sulfonyl group could replace the methylene linker in compound (**33**). By reacting compound (**18**) or (**19**) with benzenesulfonyl chloride, compounds (**45**) and (**46**) were obtained in good yields. Similarly, treatment of compound **18** with 2,6-difluorobenzoyl chloride provided the

1-(2,6-difluorobenzoyl)-2-(2,6-difluorophenyl)benzimidazole (**47**), allowing the testing of carbonyl as a linker. In addition, the introduction of nitrogen into the N1-benzyl ring by synthesizing the 3-pyridyl derivative (**43**) via alkylation with α-bromo-methylpyridine was investigated.

Synthesis And Biological Activity of 4-, 5-, 6- And 7-Substituted Benzimidazoles

In addition to the 1,2-substituted benzimidazoles described above, 4-, 5-, 6-, and 7-mono- and di-substitutions of 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole, and its des-methyl analog (**26**), were synthesized and their properties observed. On the basis of inhibition of HIV-1 cytopathic effect (*i.e.*, protection from cell killing in the assay described in Example 91), it was determined that C-4 substituted analogs were consistently the most active compounds, as long as the substitution did not introduce strong electron withdrawing groups. Although it was less active, the 6-substituted analogs of **33** also exhibited desired activity. However, the 5- or 7-substituted analogues of **33** showed decreased RT inhibition.

Variation of the benzimidazole ring portion of **33** was accomplished mostly through determining and then using the appropriate choice of starting material. The general approach utilized in the synthesis of the desired substituted 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazoles is outlined in Figure 14. As regiocontrolled benzylation of C-2 substituted benzimidazoles was not expected for 5-, 6- or 7-substituted benzimidazoles, in order to control the regiochemistry, the *N*-acyl-nitroanilines were alkylated before reductive cyclization. In Figure 14, "a" comprises 2,6-difluorobenzoyl chloride/pyridine/THF (1:1); "b" comprises NaOH (sodium hydroxide)/MeOH (methanol)/dioxane; "c" comprises Br_2 (bromine)/pyridine/THF; "d" comprises 2,6-F_2BnBr/NaH/THF; and "e" comprises Fe/AcOH.

As indicated in Figure 14, it was determined that acylation of a number of substituted nitroanilines with 2,6-difluorobenzoyl chloride (**7**) could yield the desired substituted *N*-(2,6-difluorobenzoyl)nitroanilines. In the case of the 4- or 5-chloro-nitroanilines, the predominate product was however found to be the bis-*N*-acylated products, **400** and **600**. A variety of conditions involving time, temperature, the number of equivalents of reactants and the concentration were examined in order to identify suitable conditions for production of desired compounds. Unfortunately, appropriate conditions were not found that yielded the desired mono-acylated products, **500** and **700**. However, it was fortunately determined that the mono-*N*-acyl-nitroaniline products could be obtained in high yields by selective de-acylation using NaOH in MeOH and dioxane. In most cases, alkylation of the *N*-acyl-nitro-aniline

intermediates, **500** or **700** with 2,6-difluoro-α-bromo-toluene produced high yields of the desired *N*-(2,6-difluorobenzyl) products. The *N*-acyl-*N*-(2,6,-difluorobenzyl)nitroanilines were subsequently reductively cyclized under similar conditions employed in the development of the 1- and 2- substituted compounds.

Synthesis of 1-(2,6-difluorobenzoyl)-4-bromo-nitroanilide **1200** was accomplished by bromination of 1-(2,6-difluorobenzoyl)nitroanilide (**11**). Benzylation and reductive cyclization as done with the 4-chloro derivative was found to provide 5-bromo-1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole, **2100**, in good yields. Synthesis of 5-nitrobenzimidazole, **2900**, made use of 2-(2,6-difluorophenyl)benzimidazole, as described above. Mono-nitration of 2-(2,6-difluorophenyl)benzimidazole with nitric acid at room temperature yielded 5-nitro-benzimidazole **2900** as the only product. It was subsequently determined that alkylation with 2,6-difluoro-α-bromo-toluene occurred regiospecifically to yield the 5-nitro-1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole, **3200**. Preparation of 4,5-dimethylbenzimidazole **2700** was accomplished starting from 2,3-dimethyl-6-nitroaniline. Benzylation with 2,6-difluoro-α-bromo-toluene was observed to occur regiospecifically due to the presence of 4-methyl group to yield **3000**.

Although an understanding of the mechanism is not necessary for the production and use of the present invention, mono acylation of 3-nitro-1,2-phenylenediamine with 2,6-difluorobenzoyl chloride (7), yielded a single product that was presumed to be the *N*-(2,6-difluorobenzoyl)-2-amino-3-nitroanilide, **800**, on the assumption that acylation occurred at the less hindered C-1 amino. Since cyclization of *N*-1 or *N*-2 acylated product would lead to the desired 2-aryl-benzimidazole, detailed regiochemical analysis was not carried out. In contrast to all the previous reductive ring closures, cyclization of **800** was accomplished solely in the presence of refluxing acetic acid to yield 2-(2,6-difluorophenyl)-4-nitrobenzimidazole, **2800**. Alkylation of **2800** with 2,6-difluoro-α-bromo-toluene provided a key intermediate in the preparation of a number of 4-substituted benzimidazole derivatives.

As shown in Figure 15, reduction of the 4-nitro group of **3100** was accomplished with tin (II) chloride. In this Figure, "a" comprises 2,6-difluorobenzoyl chloride/pyridine/THF (1:1); "b" comprises AcOH/reflux; "c" comprises 2,6-F_2-BnBr/NaH/THF; "d" comprises $SnCl_2$/AcOH/HCl; "e" comprises Ac_2O (acetic anhydride)/THF; "f" comprises H_2CO (formaldehyde)/$NaBH_4$ (sodium borohydride)/H_2SO_4; and "g" comprises $NaNO_2$ (sodium nitrite)/HBr (hydrogen bromide) or HCl.

Compound **3300** was used to prepare the 4-bromo, **3400**, and 4-chloro, **3500**, benzimidazoles via Sandmeyer reactions (*i.e.*, methods known in the art). The 4-*N*-acetamido, **3600**, was prepared by mono-acylation of **3300** with acetic anhydride. Treatment of **3300** with formaldehyde and sodium borohydride yielded the dimethylamino compound, **3700**.

RT Inhibition By 1 And 2- Substituted Benzimidazoles

The testing of the 2-aryl-1-(2,6-difluorobenzyl)benzimidazoles for their HIV-1 RT inhibition activity indicated that a number of aromatic systems were tolerated at the C2 position. These results are shown in Figures 5 and 7. In this Figure, the IC_{50}(μM) column indicates the quantity of drug required to reduce WT RT enzyme activity by 50% (IC_{50}).

As shown in Figure 7, the ability to inhibit wild type RT (WTRT) by the hydrogen (**49**), methyl (**35**), hydroxymethyl (**48**), isopropyl (**34**), formyl (**50**), phenyl (**39**), and bis-2,6-difluorobenzyl (**32**) compounds was measured as the percent inhibition of nucleotide incorporation into an rC-dG template primer at 10 μmolar drug concentration. Except for compound **39**, where the C2 was phenyl, all the substituents at the 2 position failed to appreciably inhibit HIV-1 RT. Substitution of the phenyl with fluorine at the 2- and 6-positions yielded the best inhibitor, compound **33** (IC_{50}=200 nM).

Results included in Figure 8 for TIBO and TZB are in contrast with those reported by Pauwels *et al.* (Pauwels *et al.*, "New Tetrahydroimidazo[4,5,1-jk][1,4]-Benzodiazepin-2(1H)-One and Thione Derivatives are Potent Inhibitors of Human Immunodeficiency Virus type 1 Replication and are Synergistic with 2',3'-Dideoxynucleoside Analogs," *Antimicrob. Agents Chemother.*, 38:2863-2870 [1994]), who reported an IC_{50} for rC:dG of 0.06 μM for TIBO, and Buckheit *et al.* (Buckheit *et al.*, "Thiazolobenzimidazole: Biological and Biochemical Anti-retroviral Activity of a New Nonnucleoside Reverse Transcriptase Inhibitor," *Antiviral Res.*, 21:247-265 [1993]), who reported an IC_{50} for rC:dG of 0.5 μM for ribosomal RNA.

Although knowledge of the precise mechanism is not necessary to successfully practice the invention, it is contemplated that because the fluorines do not dramatically alter the size of the 2-phenyl ring, the four-fold increase in inhibitory activity observed from compounds **39** to **26** probably represented some alteration in the aromatic interactions between the 2,6-difluorophenyl ring, and the aromatic side chain residues surrounding the NNRTI binding pocket. Less conservative changes, such as the addition of an ortho-methyl to the 2-phenyl ring, led to a two-fold decrease in RT inhibition (*See, e.g.*, **36**). This decrease in RT inhibition led to the examination of other planar aromatic systems. For example, changing the

2-phenyl to the 4-pyridyl resulted in almost no change in the IC_{50} value. (*See*, *e.g.*, compounds **39** and **41**). These results indicated that some heteroaromatic systems can be introduced at C2 without penalty. However, compound **40** (*i.e.*, the 3-pyridyl compound) showed considerably less activity. While it is again not necessary to understand precise mechanisms in order to use the various embodiments of present invention, it is possible that the lone pair of electrons on the 4-pyridyl system can be accommodated, in contrast to the use of the 3-pyridyl compound, in which unfavorable interactions result. Larger aromatic moieties at C2 (*e.g.*, naphthyl), regardless of orientation, were found to result in complete loss of inhibitory activity, indicating that there was a limit to the size of the inhibitor the NNRTI binding pocket can accommodate. These observations are shown in Figure 5.

As shown in Figure 6, the benzenesulfonyl and 2,6-difluorobenzoyl derivatives (**45**, **46**, and **47**) did not show appreciable RT inhibition activity. Substitution on the phenyl ring by a pyridine ring (**48**) similarly led to lower inhibition (*See*, Figure 7). Removal of the fluorine at the 2 and 6 position (**28** or **29**), or its replacement with chlorine (**30**) also resulted in a decrease in inhibition. Likewise, addition of more fluorines on the benzyl ring (**42**) yielded a compound showing greatly decreased inhibition activity (*See*, Figure 6).

Testing Of 4,5 And 5,6-Disubstituted And Mono-Substituted Benzimidazoles Against Reverse Transcriptase

Testing of the 4,5, and 5,6- di-substituted, and mono-substituted benzimidazoles was determined by measuring the relative nucleotide incorporation using an rC-dG template primer at 1 μmol drug concentration (10-fold lower than used above), to the amount of incorporation with no inhibitor present utilizing WT HIV-1 RT. As seen in Figure 16, most of the methyl derivatives inhibited RT activity in this enzyme based assay. In these tests, the enzyme assay was conducted with WT RT. Although it is not necessary to understand precise mechanisms in order to use the present invention, a change in % inhibition was noted as the methyl group is moved from the 4 to 7 positions. In the case of the 5- and 7-methyl derivatives, the % inhibition is dramatically decreased from the 4- and 6-methyl derivatives. The observed decrease determined for the 7-methyl might be due to the adoption of a different conformation from the 4-methyl owing to steric interactions between the 7-methyl and the N-1 benzyl group. Since the 5-methyl derivative, **2400**, can assume similar conformations as the 4-methyl derivative, **100**, and the 6-methyl derivative, **2500**, the decrease in % inhibition determined for the 5-methyl compound presumably must be due to differences in inductive

effects. In the case of **3000**, with 4,5-dimethyl groups, the significant inhibition found with **100** possessing a single methyl at C-4 was dramatically decreased by the presence of the C-5 methyl.

It is was also observed that substitution at C-5 led to consistently less inhibition no matter what substitutent was examined, as shown in Figure 17. In comparing the 4-, 5-, and 6- chloro compounds, the 5-chloro shows approximately two-fold more activity than either the 4- or 6-chloro compounds, **3500** or **2300**. A similar decrease is found when comparing the 4-bromo, **3400**, with the 5-bromo, **2100**. Even though the total inhibition was decreased by the presence of a strong withdrawing substitutent, this trend was also evident with the 4-nitro, **3100**, and 5-nitro, **2900**. These data led to further examination of the substitution at the C-4 position.

As seen in Figure 18, most of the 4-substituted benzimidazoles synthesized were able to inhibit RT in an assay utilizing WT RT enzyme. Three methods for the measurement of the inhibition of HIV-1 WT RT were used: i) the relative inhibition of nucleotide incorporation into a rC-dG template primer at 1 μmol drug concentration compared with the amount of incorporation with no inhibitor present; ii) the drug concentration required to inhibit 50% of nucleotide incorporation into a rC-dG template primer by HIV-1 WT RT (IC_{50}); and iii) the drug concentration required to reduce cell killing or virus production of HIV-1 WT RT by 50% (EC_{50}).

The most potent inhibitor of HIV-1 WT RT by all three measurements of RT inhibition was the 4-methoxyl (IC_{50}= 0.0073 μM and EC_{50}= 0.0046 μM). The IC_{50} for the 4-methoxyl is 100-fold more potent than the IC_{50} for TZB and TIBO and is comparable to those determined for 8-Cl TIBO and nevirapine. Although the 4-methyl, 4-amino and 4-*N*-methylacetamido compounds all have similar IC_{50} values (IC_{50}= 0.20 μM, 0.28 μM, and 0.32 μM, respectively), the 4-N-methylacetamido compound is 20-fold more potent than the 4-methyl or 4-amino compounds as determined by the cytopathic cell killing assay (EC_{50}= 0.02 μM).

Cytopathic Cell Killing Assay

In depth biological evaluation of the RT inhibitory properties of the most active 4-substituted compounds was determined with cultured MT-4 cells infected with WT and HIV-1 variants containing amino acid substitutions in RT, as described in Example 91 (*See*, Yang et al., "Characteristics of a Group of Nonnucleoside Reverse Transcriptase Inhibitors

with Structural Diversity and Potent Anti-Human Immunodeficiency Virus Activity," *Leukemia* 9:S75-S85 [1995]). The cross-resistance profile of the different compounds are found in Figures 8, 19 and 32. In these Figures, antiviral data are reported as the quantity of drug in μM required to reduce cell killing or virus production by 50% (EC_{50}). The various HIV isolates tested in the Figures are those corresponding to wild-type virus (NL4-3) and the other strains listed by their RT mutations. The three 4xAZT isolates included in the Figures represent AZT drug-resistant variants. For example, the 4xAZT/L100I isolate has five mutations: four mutations confer increased resistance to AZT, and the other mutation is located within the NNRTI binding pocket. TZB and nevir. (nevirapine) are two well-known NNRTIs, included in this experiment for comparison purposes. As shown in Figure 8, the 4-methyl derivative **33** was consistently 3- to 4-fold better in the inhibition of the various viral isolates examined than the des-methyl analog **26**. The increased inhibition observed for **33** suggested that substituents on the benzimidazole ring can significantly improve binding of this class of compounds to the NNRTI binding pocket residues.

Figure 19 shows the cross-resistance profile with NNRTI-resistant HIV isolates from the cytopathic cell killing assay for a number of 4-substituted compounds (the methoxyl, *N*-methylacetamido, ethyl, chloro, amino, *N*-acetamido, and *N*-methylamino derivatives), as well as, TZB and nevirapine. The methoxyl, *N*-methyl acetamido, ethyl, chloro, amino, *N*-acetamido, and *N*-methyl amino derivatives were all found to inhibit HIV-1 better than TZB in the cytopathic cell killing assay. In the case of the methoxyl and N-methylacetamido derivative the cross-resistance profile was equal or better against the various variants than nevirapine, the only nonnucleoside inhibitor currently approved by the FDA for the treatment of AIDS. The only variant that showed no inhibition for the different compounds tested was the K103N isolate which also renders TZB and nevirapine ineffective.

Figure 32 shows the effect of substitution of the N-1 position on the ability to inhibit some NNRTI-resistant HIV isolates. Substitution of the 2,6-difluorobenzyl group by the prenyl side chain found in TIBO was seen to decrease the inhibitory activity for the V108I and Y181C variants.

Figures 20, 21, and 22 indicate the therapeutic index for three embodiments of the present invention. The therapeutic index is the difference between efficacy of the drug and cellular toxicity. In the case of compound **33**, the 4-methyl derivative, the therapeutic index at 50% (TC_{50}) was greater than one log in concentration.

In summary, the methoxyl and N-methylacetamido compounds were found to possess the best overall biological profile of this series. These two embodiments were determined to inhibit many of the known clinically relevant non-nucleoside amino acid variants of HIV-1. It is contemplated that other substitutions or different attachment sites may result in further optimization of the compounds of the present invention. The present invention provides significant advantages over drugs such as TZB and nevirapine, as it retains activity against HIV mutants that have lost sensitivity to these drugs (e.g., the V106A, Y181C, and Y188C isolates).

Geometry Of TZB And 1-(2,6-Difluorobenzyl)-2-Phenylbenzimidazole

Semi-empirical quantum mechanical minimization at the AM1 level was used to compare the geometry of TZB and 1-(2,6-difluorobenzyl)-2-phenylbenzimidazole (**39**). As shown in Figure 9, considerable similarity was observed between the energy minimized "butterfly-like" shapes of TZB and **39**. For TZB, the "butterfly-like" shape was previously determined by X-ray and NMR methods. (*See*, A. Chimirri *et al.*, "Thiazobenzimidazoles as Non-Nucleoside HIV-1 RT Inhibitors," Abst. II Congresso Congiunto Italiano-Spagnolo di Chimica farmaceutica," Ferrara, Italy, August 30-September 3, 1995, ML20). For **39** in contrast to TZB, more than one "butterfly-like" conformation can be adopted by rotation of the molecule's benzyl side chain. Although the C2 phenyl of the AM1 energy-minimized molecule **39** does not overlap the thiazolo ring of TZB, at least two higher energy rotational isomers result in almost complete overlap. Although X-ray analysis is required to predict the correct "butterfly-like" orientation of this compound with RT and the NNRTI binding pocket, some of the predominant contributions to the binding of NNRTI to RT involve π stacking and hydrophobic interactions. The extra aromatic ring present in **39** might significantly influence these interactions. This ability of HIV-1 RT to accommodate extra phenyl rings resulted in investigation of additional aromatic moieties.

Purity Of The Substituted Benzimidazoles

The active benzimidazole compounds of the present invention were produced at a very high purity level. As shown in Figures 25, the carbon, hydrogen and nitrogen analyses (CHN values) of these compounds were very close to the predicted values. CHN analysis (*i.e.*, elemental analysis) as known to those in the art, determines the amount of the elements in accurately weighed samples of the compound, and matches them against the amounts

predicted from the elemental formulae. Correspondence of experimental with the predicted values to within 0.3% indicates high levels of purity.

EXPERIMENTAL

The following examples are provided in order to demonstrate and further illustrate certain preferred embodiments and aspects of the present invention and are not to be construed as limiting the scope thereof. Although embodiments have been described with some particularity, many modifications and variations of the preferred embodiment are possible without deviating from the invention.

In the experimental disclosure which follows, the following abbreviations apply: PBS (phosphate buffered saline); MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide): EDTA (ethylenedinitrotetraacetic acid disodium salt); HCl (hydrogen chloride); Tris (triphenylphosphine); $AlMe_2NH_2$ (dimethylaluminum amine); NaH (sodium hydride); $NaNO_2$ (sodium nitrite); NaOH (sodium hydroxide); KOH (potassium hydroxide); $KMnO_4$ (potassium permanganate); NaCl (sodium chloride); CuCl (copper chloride); SDS (sodium dodecyl sulfate): $NaHSO_4$ (sodium bisulfate); $Na_2S_2O_3$ (sodium thiosulfate); Na_2SO_4 (sodium sulfate); TAE (Tris-Acetate-EDTA); $MeOH/CH_2Cl_2$ (methanol/dichloromethane); $FeSO_4$ (ferrous sulfate); $CuSO_4$ (cuprous sulfate); $MgSO_4$ (magnesium sulfate); NaOAc (sodium acetate); DMF (dimethyl formamide); THF (tetrahydrofuran); $NaHCO_3$ (sodium bicarbonate); Na_2CO_3 (sodium carbonate): HBr (hydrogen bromide); H_2SO_4 (sulfuric acid); H_2CO (formaldehyde); KBr (potassium bromide); DMSO (dimethyl sulfoxide); DMSO-d_6 (fully deuterated dimethyl sulfoxide): $CHCl_3$ (chloroform); $CDCl_3$ (deuterated chloroform); CD_2Cl_2 (deuterated methylene chloride); CD_3OD (deuterated methanol); NH_3 (ammonia); Ph (phenyl; C_6H_5) Ac (ethanoate group); AcOH (acetic acid); Et_2O (diethyl ether); EtOAc (ethyl acetate); CrO_3 (chromium trioxide); $SnCl_2x2H_2O$ (tin (II) chloride); C (carbon); H (hydrogen); N (nitrogen); CPE (cytopathic effect); ppm (parts per million); [α] (specific rotation); μL (microliters); μg (micrograms); mL (milliliters); L (liters); mg (milligrams); g (grams); hr or h (hours); mM (millimolar); M% (mole percent); μM (micromolar); nM (nanomolar); N (normal); nm (nanometers); min (minutes); mm (millimeter); kg (kilograms); δ (chemical shift); J or J (coupling constant); s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); vs (very strong); s (strong); m (medium); w (weak); vw (very weak); v (variable); mp (melting point); c (optical path length); NMR (Nuclear Magnetic Resonance); IR (Infrared Spectroscopy); MHz (megahertz); Hz (hertz); cm^{-1} (wavenumbers); eq (equivalents); M (Molar); μM

(micromolar); N (Normal); mol (moles); mmol (millimoles); μmol (micromoles); nmol (nanomoles); g (grams); mg (milligrams); μg (micrograms); ng (nanograms); l or L (liters); ml (milliliters); μl (microliters); cm (centimeters); mm (millimeters); μm (micrometers); nm (nanometers); °C (degrees Centigrade); Ci (Curies); mCi (milliCuries); mp (melting point); TZB (1-(2,6-difluorophenyl)-1H,3H-thiazolo[3,4-a]benzimidazole; RT (reverse transcriptase); WT (wild type); AZT (3'-azido-3'-deoxythymidine); NNRT (non-nucleoside reverse transcriptase); NNRTI (non-nucleoside reverse transcriptase inhibitors); BSA (bovine serum albumin); Et (ethyl); CHAPS (3-[(3-cholamidopropyl)dimethylammonio]-1-propane-sulfonate); ddC (2',3'-dideoxycytidine); TIBO (4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one; THF (tetrahydrofuran); *t*- (tert); *t*-BDMSCl (*t*-butyldimethylsilylchloride); TBDMS (*t*-butyldimethylsilyl); IC_{50} (inhibitory concentration, 50%); EC_{50} (median effective concentration); Varian (Varian Analytical Instruments, San Fernando, CA); Sigma (Sigma Chemical Co., St. Louis, MO); and Aldrich (Aldrich Chemical Company, Inc., Milwaukee, WI).

Unless otherwise indicated, all chemicals and reagents were obtained from commercially available sources, such as Sigma and Aldrich. Where analyses are indicated by symbols of the elements, the observed results were within 0.4% of the theoretical values. Melting points were determined on an electrothermal apparatus using the supplied, stem-corrected thermometer and read, per methods known in the art. NMR spectra were recorded on a Varian 200 or 300 MHz spectrometer, with Me_4Si as the internal standard. Merck silica gel (70-230 mesh and 230-400 mesh) were used for gravity and flash chromatography, respectively. Primes used in NMR assignments are defined by R' and R'' in the structures shown in Figure 3.

EXAMPLE 1

Preparation Of 2-Hydroxymethylbenzimidazole

In this Example, 2-hydroxymethylbenzimidazole (**2**) was prepared by stirring *o*-phenylenediamine (**1**)(1.3 g, 12 mmol), and 85% glycolic acid (2.74 g, 36 mmol, 300 M%), in 4 N HCl (40 mL), under reflux for 4 hours. After cooling to room temperature, the pH was adjusted to 7, with NaOH. The resulting crystals were filtered, washed with water and dried *in vacuo* (0.71 g, 4.8 mmol, 40% yield). ^{1}H-NMR (300 MHz; DMSO-d_6): δ 7.48 (m, 2H, $H_{4,7}$), 7.13 (m, 2H, $H_{5,6}$), 5.67 (t, J=5.5 Hz, 1H, OH), 4.68 (d, J=5.5 Hz, 2H, CH_2).

EXAMPLE 2

Preparation Of 2-Hydroxymethyl-4-Methylbenzimidazole

In this Example, 2-hydroxymethyl-4-methylbenzimidazole (**4**) was prepared by stirring 2,3-diaminotoluene (**3**) (2.65 g 21.7 mmol), and 85% glycolic acid (8.20 g, 107.8 mmol, 500 M%) in 4 N HCl (80 mL), under reflux for 2 hours. After cooling to room temperature, the pH was adjusted to 7 with NaOH. The resulting brown precipitate was filtered, washed with water, and dried *in vacuo* (2.97 g, 18.3 mmol, 84% yield). ^{1}H-NMR (200 MHz. DMSO-d_6): δ 7.28 (br d, 1H, H_7), 6.98 (dd, J=8.0, 7.3 Hz, 1H, H_6), 6.90 (m, 1H, H_5), 4.67 (s, 2H, CH_2), 2.49 (s, 3H, CH_3).

EXAMPLE 3

Preparation Of 2-(*t*-Butyldimethylsilyloxymethyl)-4-Methylbenzimidazole

In this Example, 2-(*t*-Butyldimethylsilyloxymethyl)-4-Methylbenzimidazole (**5**) was prepared by dissolving 2-hydroxymethyl-4-methylbenzimidazole (**4**) (1.50 g, 9.24 mmol) in pyridine (30 mL). To this mixture, *t*-BDMSCl (2.35 g, 15.6 mmol, 170 M%) was added. After 4 hours at room temperature, the reaction was concentrated to dryness. The residue was re-dissolved in CH_2Cl_2, and washed with $NaHCO_3$ (sat. aq.), and NaCl (sat. aq.), dried Na_2SO_4, filtered and concentrated. The product was purified by flash chromatography, eluting with 4% MeOH/CH_2Cl_2, and then re-crystallized from hexane (2.15 g, 7.78 mmol, 84% yield), to a white powder. ^{1}H-NMR (300 MHz, CD_3OD): δ 7.36 (br d, J=11.1 Hz, 1H, H_7), 7.11 (dd, J=11.1, 10.4 Hz, 1H, H_6), 7.01 (br d, J=10.4 Hz, 1H, H_5), 4.94 (s, 2H, CH_2O), 2.55 (s, 3H, CH_3), 0.95 (s, 9H, Si*t*-Bu), 0.14 (s, 6H, $Si(CH_3)_2$).

EXAMPLE 4

Preparation Of 2-Isopropyl-4-Methylbenzimidazole

In this Example, 2-isopropyl-4-methylbenzimidazole (**6**) was prepared by dissolving 2,3-diaminotoluene (**3**) (1.00 g, 8.19 mmol), and isobutyric acid (4.0 mL, 43.1 mmol, 525 M%), in 4 N HCl (90 mL). After 2 hours at reflux, the reaction was cooled in an ice bath, and the pH adjusted to 7 with NaOH. The resulting precipitate was filtered and washed with water. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 12.02 (br, 1H, NH), 7.26 (br, 1H, H_7), 6.99 (dd,

J=7.4, 7.7 Hz, 1H, H_6), 6.87 (ddt, J=-0.8, 1.1, 7.4 Hz, 1H, H_5), 3.14 (sep, J=7.0 Hz, 1H, iPr), 2.48 (s, 3H, CH_3), 1.34 (d, J=7.0 Hz, 6H, iPr).

EXAMPLE 5

Preparation of *N*-(2,6-Diflurobenzoyl)-2-Nitroanilide

In this Example, *N*-(2,6-diflurobenzoyl)-2-nitroanilide (**10**) was prepared using "Method A." First, 2-nitroaniline (**8**) (1.1 g, 8.0 mmol) was dissolved in THF (10 mL) and pyridine (2 mL). Then, 2,6-difluorobenzoyl chloride (7) (1.11 mL, 8.8 mmol, 110 M%) dissolved in THF (15 mL) was added to the first mixture. After stirring for 5 hours at room temperature, the reaction was concentrated to dryness. The residue was re-dissolved in ethylacetate, and washed with $NaHSO_4$ (5% solution), $NaHCO_3$ (sat. aq.), and NaCl (sat. aq.). The organic layer was dried under Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was recrystallized from ethylacetate/hexane, to produce crystals that were slightly yellow (1.7 g, 6.1 mmol, 76%), with a melting point of 139°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 10.77 (s, 1H, NH), 8.89 (dd, J=1.2, 8.5 Hz, 1H, H_3), 8.26 (dd, J=1.5, 8.5 Hz, 1H, H_6), 7.75 (ddd, J=1.2, 7.9, 8.5 Hz, 1H, H_5), 7.50 (m, 1H, H_4), 7.29 (ddd, J=1.5, 7.9, 8.5 Hz, 1H, H_4), 7.07 (m, 2H, $H_{3',5'}$).

EXAMPLE 6

Preparation Of *N*-(2,6-Difluorobenzoyl)-2-Methyl-6-Nitroanilide

In this Example, *N*-(2,6-difluorobenzoyl)-2-methyl-6-nitroanilide (**11**) was prepared using Method A. 2-methyl-6-nitroaniline (**9**) (2.25 g, 14.8 mmol) and 2,6-difluorobenzoyl chloride (7) (1.9 mL, 15 mmol, 100 M%) were mixed and stirred overnight. The solution was purified by gravity chromatography, and eluted with CH_2Cl_2/hexane/diethylether (380-120-10). The product was 2.36 g (8.1 mmol, 55% yield) of slightly yellow crystals. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.55 (s, 1H, NH), 7.87 (dd, J=8.2, 0.92 Hz, 1H, H_5), 7.61 (d, J=7.4 Hz, 1H, H_3), 7.48 (m, 1H, H_4), 7.38 (dd, J=7.4, 8.2 Hz, 1H, H_4), 7.05 (m, 2H, $H_{3',5'}$), 2.43 (s, 3H, CH_3).

EXAMPLE 7

Preparation Of *N*-Isonicotinoyl-2-Methyl-6-Nitroanilide

In this Example, *N*-isonicotinoyl-2-methyl-6-nitroanilide (**12**) was prepared using Method A. 2-methyl-6-nitroaniline (**9**) (1.52 g, 10.0 mmol), and isonicotinoyl chloride hydrochloride (2.95 g, 19.7 mmol, 200 M%) were stirred together for 4 hours. A second addition of isonicotinoyl chloride hydrochloride (1.05 g, 5.90 mmol, 60 M%) was added, and the solution was stirred overnight. The preparation was re-crystallized from diethylether/hexane (3:1) to produce 1.61 g (6.26 mmol, 53% yield) of white powder. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 9.06 (br, 1H, NH), 8.82 (m, 2H, $H_{2',6'}$) 7.93 (br d, 7.9 Hz, 1H, H_6), 7.77 (m, 2H, $H_{3',5'}$), 7.63 (br d, J=8.0 Hz, 1H, H_3), 7.40 (dd, J=7.9, 8.0 Hz, 1H, H_4).

EXAMPLE 8

Preparation Of *N*-(2-Methylbenzoyl)-2-Nitroanilide

In This Example, *N*-(2-methylbenzoyl)-2-nitroanilide (**13**) was prepared by Method A, by mixing 2-nitroaniline (**8**) (1.28 g, 9.3 mmol) and *o*-toluoyl chloride (1.52 mL, 11.6 mmol, 125 M%), and then recrystallized with ether/hexane (1:1) to produce 2.2 g (8.6 mmol, 92% yield) of yellow crystals of *N*-(2-methylbenzoyl)-2-nitroanilide. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 10.75 (s, 1H, NH), 8.98 (d, J=8.5 Hz, 1H, H_3), 8.27 (d, J=8.5 Hz, 1H, H_6), 7.72 (dd, J=8.5, 7.4 Hz, 1H, H_5), 7.61 (d, J=8.4 Hz, 1H, H_6), 7.41 (dd, J=8.5, 7.4 Hz, 1H, H_4), 7.32 (t, J=7.4 Hz, 1H, H_4), 7.31 (d, J=7.4 Hz, 1H, H_3), 7.23 (dd, J=8.4, 7.4 Hz, 1H, H_5), 2.56 (s, 3H, CH_3).

EXAMPLE 9

Preparation Of *N*-(1-Naphthoyl)-2-Methyl-6-Nitroanilide

In this Example, *N*-(1-naphthoyl)-2-methyl-6-nitroanilide (**14**) was prepared by Method A, by mixing 2-methyl-6-nitroaniline (**9**) (1.52 g, 10.0 mmol) and 1-naphthoyl chloride (2.00 mL, 13.3 mmol, 130 M%). After one hour of stirring at room temp, a second volume of 1-naphthoyl chloride (1.0 mL, 6.65 mmol, 66 M%) was added. The mixture was stirred for 6 hours and recrystallized with ethyl acetate to produce 2.79 g (9.11 mmol, 91% yield) of white powder. ^{1}H-NMR (200 MHz, CD_2Cl_2): δ 8.09-7.99 (m, 2H), 7.77 (m, 1H), 7.66-7.41 (m, 5H), 7.23 (d, J=8.3 Hz, 1H), 7.24 (dd, J=7.3 Hz, 1H), 2.77 (s, 3H, CH_3).

EXAMPLE 10

Preparation Of *N*-(2-Naphthoyl)-2-Methyl-6-Nitroanilide

In this Example, *N*-(2-naphthoyl)-2-methyl-6-nitroanilide (**15**) was prepared according to Method A, by mixing 2-methyl-6-nitroaniline (**9**)(1.52 g, 10.0 mmol) and 2-naphthoyl chloride (2.00 mL, 13.3 mmol, 130 M%). After 1 hour of stirring, a second volume of 2-naphthoyl chloride (1.0 mL, 6.65 mmol, 66 M%) was added. The mixture was stirred for 6 hours and recrystallized with ethyl acetate to produce 2.29 g (7.48 mmol, 75% yield) of white powder. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 9.15 (br s, 1H, NH), 8.49 (s, 1H, $H_{1'}$), 8.06-7.86 (m, 5H, nap & H_5), 7.72-7.45 (m, 3H, nap & H_3), 7.37 (dd, J=7.73 Hz, 1H, H_4), 2.43 (s, 3H, CH_3).

EXAMPLE 11

Preparation Of *N*-Nicotinoyl-2-Methyl-6-Nitroanilide

In this Example, *N*-Nicotinoyl-2-methyl-6-nitroanilide (**16**) was prepared by Method A, by mixing 2-methyl-6-nitroaniline (**9**)(1.52 g, 10.0 mmol) and nicotinoyl chloride hydrochloride (2.67 g, 15.0 mmol, 150 M%). After stirring overnight and recrystallization from diethylether/hexane (3:1) 1.41 g (5.49 mmol, 55% yield) of white powder were produced. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 9.16 (dd, J=0.8, 2.2 Hz, 1H, H_2), 9.01 (br, 1H, NH), 8.80 (dd, J=1.7, 4.8 Hz, 1H, H_6), 8.23 (ddd, J=1.7, 2.2, 8.0 Hz, 1H, H_4), 7.92 (m, 1H, H_5), 7.62 (br d, J=7.5 Hz, 1H, H_3), 7.48 (ddd, J=0.8, 4.8, 8.0 Hz, 1H, H_5), 7.39 (dd=7.5, 8.5 Hz, 1H. H_4), 2.39 (s, 3H, CH_3).

EXAMPLE 12

Preparation Of 2-(2,6-Difluorophenyl)benzimidazole

In this Example, 2-(2,6-difluorophenyl)benzimidazole (**18**) using Method B. First, 2-methyl-6-nitroaniline (**9**) (9.31 g, 31.9 mmol) was dissolved in glacial acetic acid (100 mL). Iron powder (**17**) (4.95 g) was then added. After 30 min at reflux, the reaction was concentrated to dryness, eluting with ethylacetate and washed with $NaHCO_3$. The aqueous layer was back extracted with ethylacetate and the combined organic solution was washed with $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.), dried (Na_2SO_4), filtered and concentrated. The

product was recrystallized from ethylacetate (6.24 g, 27.1 mmol, 85% yield of white powder). ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 9.92 (br, 1H, NH), 7.69 (br, 1H, $H_{4,7}$), 7.45 (m, 1H, H..), 7.31 (ddd, J=3.2, 4.0, 6.0 Hz, $H_{5,6}$), 7.11 (m, 2H, $H_{3',5'}$).

EXAMPLE 13

Preparation Of 2-(2,6-Difluorophenyl)-4-Methylbenzimidazole

In this Example, 2-(2,6-difluorophenyl)-4-methylbenzimidazole (**19**) was produced using Method B. *N*-(2,6-difluorobenzoyl)-2-methyl-6-nitroanilide (**11**) (1.35 g, 4.62 mmol) and iron powder (**17**) (1.3 g) mixed as described for Method B. After recrystallization from diethylether/hexane (3/1) 1.1 g (4.48 mmol, 97%) of colorless crystals were produced, with a melting point of 148°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.86 (s, 1H, NH), 7.66 (m, 1H, $H_{4'}$), 7.33 (m, 2H, $H_{3',5'}$), 7.27-7.18 (m, 1H, H_7), 7.15 (dd, J=8.0, 7.2 Hz, 1H, H_6), 7.05 (d, J=7.2 Hz, 1H, H_5), 2.55 (s, 3H, CH_3).

EXAMPLE 14

Preparation Of 2-(2-Methylphenyl)Benzimidazole

In this Example, 2-(2-methylphenyl)benzimidazole (**20**) was produced using Method B. *N*-(2-methylbenzoyl)-2-nitroanilide (**13**) (1.9 g, 7.4 mmol) and iron powder (**17**) (1.2 g) were mixed. After recrystallization from diethylether/hexane (3/1) 1.2 g (5.76 mmol, 78%) of colorless crystals were produced, with a melting point of 215°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.63 (m, 1H, $H_{6'}$), 7.58 (dd, J=6.1, 3.2 Hz, 2H, $H_{4,7}$), 7.39-7.21 (m, 3H, $H_{3',4',5'}$), 7.25 (dd, J=6.1, 3.2 Hz, 2H, $H_{5,6}$), 2.58 (s, 3H, CH_3).

EXAMPLE 15

Preparation Of 2-(1-Napthyl)-4-Methylbenzimidazole

In this Example, 2-(1-napthyl)-4-methylbenzimidazole (**21**) was produced using Method B. The 1-naphthyl derivative shown as compound **14** (2.60 g, 11.7 mmol) and iron powder (**17**) (2.00 g), was purified by flash chromatography, eluting with 4% MeOH/CH_2Cl_2 and recrystallization from diethylether/hexane (3:1) 1.63 g (6.31 mmol, 54% yield) of white powder. ^{1}H-NMR (200 MHz, CD_2Cl_2): δ 9.71 (br, 1H, NH), 8.80 (m, 1H), 8.01-7.89 (m,

2H), 7.81 (dd, J=1.3, 7.3 Hz, 1H), 7.61-7.47 (m, 4H), 7.21 (dd, J=7.3, 7.6 Hz, 1H), 7.11 (m, 1H), 2.66 (s, 3H, CH_3).

EXAMPLE 16

Preparation Of 2-(2-Napthyl)-4-Methylbenzimidazole

In this Example, 2-(2-napthyl)-4-methylbenzimidazole (**22**), using Method B. The compound shown as compound (**15**) (2.25 g, 7.34 mmol) and iron powder (**17**) (1.60 g) gave after purification by flash chromatography eluting with 4% MeOH/CH_2Cl_2 and recrystallization from diethylether/hexane (3:1), resulted in the production of 1.00 g (3.88 mmol, 53% yield) white powder. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.70 (br, 1H, NH), 8.34 (dd, J=1.7, 8.6 Hz, 1H), 7.99-7.87 (m, 3H), 7.57-7.51 (m, 2H), 7.50-7.43 (m, 1H), 7.15 (dd, J=7.3, 7.5 Hz, 1H, H_6), 7.04 (m, 1H, H_5), 2.67 (s, 3H, CH_3).

EXAMPLE 17

Preparation Of 2-(3-Pyridyl)-4-Methylbenzimidazole

In this Example, 2-(3-pyridyl)-4-methylbenzimidazole (**23**) was produced using Method B. *N*-Nicotinoyl-2-methyl-6-nitroanilide (**16**) (1.00 g, 3.89 mmol) and iron (**17**) (0.75 g) were mixed for 30 minutes. Additional iron powder (0.75 g) was then added, and the mixture prepared as described for Method B. Recrystallization from ethylacetate resulted in the production of 0.72 g (3.44 mmol, 88% yield) of white powder; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 9.38 (dd, J=2.3, 0.9 Hz, 1H, $H_{2'}$), 8.67 (dd, J=1.7, 4.8 Hz, 1H, $H_{6'}$), 8.53 (ddd, J=1.7, 2.3, 8.0 Hz, 1H, $H_{4'}$), 7.58 (ddd, J=0.9, 4.8, 8.0 Hz, 1H, $H_{5'}$), 7.44 (dd, J=0.9, 8.1 Hz, H_7), 7.12 (dd, J=7.3, 8.1 Hz, 1H, H_6), 7.02 (ddt, J=0.2, 0.9, 7.3 Hz, 1H, H_5), 2.59 (s, 3H, CH_3).

EXAMPLE 18

Preparation Of 2-(4-Pyridyl)-4-Methylbenzimidazole

In this Example, 2-(4-pyridyl)-4-methylbenzimidazole (**24**) was produced using Method B. *N*-Isonicotinoyl-2-methyl-6-nitroanilide (**12**) (1.02 g, 3.97 mmol) and iron powder (**17**) (1.10 g) were mixed as described for Method B. Recrystallization from ethylacetate

resulted in the production of 0.70 g (3.34 mmol. 84% yield) of white powder; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.75 (m, 2H, $H_{2',6'}$), 8.14 (m, 2H, $H_{3',5'}$), 7.46 (dd, J=0.9, 8.1 Hz, 1H, H_7), 7.15 (dd, J=7.3, 8.1 Hz, 1H, H_6), 7.05 (ddt, J=0.8, 0.9, 7.3 Hz; 1H, H_5), 2.59 (s, 3H, CH_3).

EXAMPLE 19

Preparation Of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)Benzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole (**26**) was prepared using Method C. The benzimidazole compound **18** (2.00 g, 8.70 mmol) and 2,6-difluoro-α-bromo-toluene (**25**) (2.85 g, 160 M%), were dissolved in THF (20 mL). To this mixture, NaH (0.75 g, 215 M%) was added. After mixing for 2 hours, the reaction was quenched with MeOH and concentrated. The residue was redissolved in ethylacetate, washed with $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.), dried (Na_2SO_4), filtered and concentrated. The product was recrystallized from ethylacetate/hexane (1:1) (2.62 g, 0.35 mmol, 85% yield of white powder), mp 145°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.77 (m, 1H, H_4), 7.54 (m, 1H, $H_{4'}$), 7.49m, 1H, H_7), 7.29 (m, 2H, $H_{5,6}$), 7.24 (m, 1H, $H_{4''}$), 7.08 (m, 2H, $H_{3',5'}$), 5.82 (m, 2H, $H_{3'',5''}$), 5.30 (s, 2H, CH_2PhF_2). Anal. ($C_{20}H_{12}F_4N_2$) C,H,N.

EXAMPLE 20

Preparation Of 1-Benzyl-2-(2,6-Difluorophenyl)Benzimidazole

In this Example, 1-benzyl-2-(2,6-difluorophenyl)benzimidazole (**28**) was produced using Method C. The benzimidazole compound **18** (100 mg, 0.43 mmol) and benzylbromide (**27**) (66.4 ml, 0.56 mmol) were mixed as indicated for Method C. After recrystallization from diethylether/hexane (3:1) 77 mg (0.24 mmol, 56%) of colorless crystals were produced, with a melting point of 124°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.88 (d, J=7.7 Hz, 1H, H_4), 7.47 (m, 1H, $H_{4'}$), 7.34-7.22 (m, 6H, $H_{5,6,7,2'',4'',6''}$), 7.07-6.99 (m, 4H, $H_{3',5',3'',5''}$), 5.28 (s, 2H, CH_2). Anal. ($C_{20}H_{14}F_2N_2$x1/8H_2O) C,H,N.

EXAMPLE 21

Preparation Of 1-Benzyl-2-(2,6-Difluorophenyl)-4-Methylbenzimidazole

In this Example, 1-benzyl-2-(2,6-difluorophenyl)-4-methylbenzimidazole (**29**) was produced according to Method C, using 2-(2,6-difluorophenyl)-4-methylbenzimidazole (**19**) (88mg, 0.33 mmol) and benzylbromide (**27**) (51 mL, 0.43 mmol) to produce, after recrystallization from diethylether/hexane (3:1), 67 mg (0.20 mmol, 61%) of colorless crystals. with a melting point of 112-117°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.46 (m, 1H, $H_{4'}$), 7.26-7.22 (m, 3H, $H_{7,3'',5''}$), 7.18-6.98 (m, 7H, $H_{5,6,3',5',2'',4'',6''}$), 5.25 (s, 2H, CH_2), 2.74 (s, 3H, CH_3). Anal. ($C_{21}H_{16}F_2N_2$x1/4H_2O) calcd. C,H,N 74.43, 4.91, 8.27; found C,H,N 74.81, 4.90, 7.85. HRMS 334.1281 (calcd) 334.1266 (found) δ ppm 4.6.

EXAMPLE 22

Preparation Of 1-(2,6-Dichlorobenzyl)-
2-(2,6-Difluorophenyl)-4-Methylbenzimidazole

In this Example, 1-(2,6-dichlorobenzyl)-2-(2,6-difluorophenyl)-4-methylbenzimidazole (**30**) was produced using Method C. In this Example, 2-(2,6-difluorophenyl)-4-methylbenzimidazole (**19**) (0.50 g, 2.05 mmol) and 2,6-dichloro-α-bromo-toluene (0.74 g, 3.08 mmol, 150 M%) were treated using Method C for 2 hours, purified by flash chromatography, eluted with 4% MeOH/CH_2Cl_2 and recrystallized from diethylether/hexane (3:1), to produce 0.70 g (1.74 mmol, 85% yield) of white powder; mp 202-203°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.48 (m, 1H, H_4), 7.26 (m, 2H, $H_{5,7}$), 7.19 (dd, J=8.0, 8.2 Hz, 1H, H_6), 7.14-6.98 (m, 5H, $H_{3',5',3'',4'',5''}$), 5.56 (s, 2H, CH_2PhCl_2), 2.64 (s, 3H, CH_3). Anal. ($C_{21}H_{14}Cl_2F_2N_2$x1/4H_2O)C,H,N.

EXAMPLE 23

Preparation Of 1-(2,6-Difluorobenzyl)-
2-*t*-Butyldimethylsilyloxymethyl-4-Methylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-*t*-butyldimethylsilyloxymethyl-4-methylbenzimidazole (**31**) was produced using Method C. In this Example, 2-(*t*-Butyldimethylsilyloxymethyl)-4-Methylbenzimidazole (**5**) (3.25 g, 11.76 mmol) and 2,6-

difluoro-α-bromo-toluene (**25**) (3.65 g, 150 M%) were treated according to Method C. for 4 h, and purified by flash chromatography with ethylacetate:hexane (1:4) to produce 4.41 g (10.96 mmol, 93% yield) of white powder. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.32 (m, 1H, $H_{4''}$), 7.17 (br d, J=8.2 Hz, 1H, H_7), 7.08 (dd, J=7.3, 8.2 Hz, 1H, H_6), 7.00 (br d, J=7.3 Hz, 1H, H_5), 6.95 (m, 2H, $H_{3'',5''}$), 5.63 (s, 2H, CH_2PhF_2), 5.13 (s, 2H, CH_2O), 2.59 (s, 3H, CH_3), 0.94 (s, 9H, Si-*tert*-Bu), 0.14 (s, 6H, $Si(CH_3)_2$).

EXAMPLE 24

Preparation Of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorobenzyloxymethyl)Benzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorobenzyloxymethyl) benzimidazole (**32**) was produced using Method C. In this Example, 2-hydroxymethylbenzimidazole (**2**) (92 mg, 0.62 mmol) and 2,6-difluoro-α-bromo-toluene (**25**) (334 mg, 1.61 mmol, 260 M%) were treated according to Method C. After recrystallization from diethylether/hexane (3:1), 66 mg (0.165 mmol, 27%) of colorless crystals were produced. with a melting point of 109°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.73 (m, 1H, H_4), 7.38 (m. 1H, H_7), 7.36-7.18 (m, 4H, $H_{5,6,4',4''}$), 6.98-6.82 (m, 4H, $H_{3',5',3'',5''}$), 5.58 (s, 2H, NCH_2PhF_2), 5.07 (s, 2H, OCH_2), 4.70 (s, 2H, OCH_2PhF_2). Anal. ($C_{22}H_{16}F_4N_2O$ x 1/2H_2O) C,H,N.

EXAMPLE 25

Preparation Of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-4-Methylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl) -4-methylbenzimidazole (**33**) was produced using Method C. The compound 2-(2,6-difluorophenyl)-4-methylbenzimidazole (**19**) (400 mg, 1.63 mmol) and 2,6-difluoro-α-bromo-toluene (**25**) (1.87 mmol, 388 mg) were treated according to Method C. After stirring overnight and recrystallization with diethylether/hexane (3:1), 453 mg (1.22 mmol, 75% yield) of white powder were produced, with a melting point of 182-186°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.48 (m, 1H, H_4), 7.32 (d, J=8.1 Hz, H_7), 7.20 (m, 1H, $H_{4'}$), 7.19 (dd, J=8.1, 7.2

Hz, 1H, H_6), 7.09 (d, J=7.2 Hz, 1H, H_5), 7.04 (m, 2H, $H_{3'\text{-}5'}$), 6.79 (m, 2H, $H_{3''\text{-}5''}$), 5.33 (s, 2H, CH_2), 2.70 (s, 3H, CH_3). Anal ($C_{21}H_{14}F_4N_2$)C,H,N.

EXAMPLE 26

Preparation Of 1-(2,6-Difluorobenzyl)-2-Isopropyl-4-Methylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-isopropyl-4-methylbenzimidazole (**34**) was prepared according to Method C, using 2-isopropyl-4-methylbenzimidazole (**6**) (0.20 g 1.15 mmol) and 2,6-difluoro-α-bromo-toluene (**25**) (0.36 g, 1.74 mmol, 150 M%) stirred for 5 h, as described, purified by flash chromatography eluted with 4% MeOH/CH_2Cl_2 and recrystallized from diethylether/hexane (3:1) to yield 0.20 g (0.67 mmol, 58% yield) of white powder, with a melting point of 151-153°C. ^{1}H-NMR (200 MHz CD_2Cl_2): δ 7.30 (m, 1H, $H_{4'}$), 7.15 (br d, J=7.7 Hz, 1H, H_7), 7.04 (dd, J=7.3, 7.7 Hz, 1H, H_6), 6.96 (br d, J=7.3 Hz, 1H, H_5), 6.82 (m, 2H, $H_{3'\text{-}5'}$), 5.38 (s, 2H, CH_2PhF_2), 3.40 (sep, J=6.8 Hz, 1H, iPr), 2.57 (s, 3H, CH_3), 1.38 (d, J=6.8 Hz, 6H, iPr). Anal. ($C_{18}H_{18}F_2N_2$)C,H,N.

EXAMPLE 27

Preparation Of 1-(2,6-Difluorobenzyl)-2-Methylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-methylbenzimidazole (**35**) was prepared according to Method C, using 2-methylbenzimidazole (204 mg, 1.54 mmol) and 2,6-difluoro-α-bromo-toluene (**25**) (351 mg, 1.70 mmol). Following recrystallization, from diethylether/hexane (3:1), 290 mg (1.12 mmol, 73%) of colorless crystals were produced, with a melting point of 99°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.66 (m, J=8.0, 1.1, 0.6 Hz, 1H, H_4), 7.37 (m, J=0.6, 1.1, 8.2 Hz, H_7), 7.30 (m, 1H, $H_{4'}$), 7.20 (m, J=8.0, 1.1, 7.3, H_5), 7.19 (m, J=8.2, 7.3, 1.1 Hz, 1H, H_6), 6.92 (m, 2H, $H_{3'\text{-}5'}$) 5.35 (s, 2H, CH_2), 2.71 (s, 3H, CH_3). Anal. ($C_{15}H_{12}F_2N_2$)C,H,N.

EXAMPLE 28

Preparation Of 1-(2,6-Difluorobenzyl)-2-(2-Methylphenyl)Benzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2-methylphenyl)benzimidazole (**36**) was produced according to Method C, using 2-(2-methylphenyl)benzimidazole (**20**) (0.10 g, 0.48 mmol) and 2,6-difluoro-α-bromo-toluene (**25**) (0.15 g, 0.73 mmol, 150 M%). Purification by flash chromatography, eluted with 2% MeOH/CH_2Cl_2, and recrystallization with diethyl ether/hexane (3:1) produced 109 mg (0.33 mmol, 68%) of colorless crystals, with a melting point of 139°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.80 (m, 1H, H_4), 7.43-7.23 (m, 7H, $H_{5,6,7,3',4',5,6'}$), 7.21 (m, 1H, $H_{4''}$), 6.79 (m, 2H, $H_{3'',5''}$), 5.31 (s, 2H, CH_2), 2.23 (s, 3H, CH_3). Anal. ($C_{21}H_{16}F_2N_2$)C,H,N.

EXAMPLE 29

Preparation Of 1-(2,6-Difluorobenzyl)-2-(1-Napthyl)-4-Methylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(1-napthyl)-4-methylbenzimidazole (**37**) was produced according to Method C, using 2-(1-napthyl)-4-methylbenzimidazole (**21**) (0.30 g, 1.16 mmol) and 2,6-difluoro-α-bromo-toluene (**25**) (0.54 g, 2.60 mmol, 225 M%). After stirring overnight and purification by flash chromatography eluting with ethylacetate/hexane (1:4) and recrystallization from diethylether/hexane (3:1), 0.32 g (0.83 mmol, 72% yield) of white powder was produced, with a melting point of 121-123°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.00 (d, J=8.1 Hz, 1H), 7.96 (d, J=8.1 Hz, 1H), 7.66 (d, J=6.3 Hz, 1H), 7.60 (t, J=7.5 Hz, 1H), 7.53 (dt, J=1.3, 7.5 Hz, 1H), 7.43 (dt, J=1.3, 7.6 Hz, 1H), 7.28 (d, J=8.1 Hz, 1H), 7.19 (t, J=7.5 Hz, 1H), 7.11 (m, 2H), 6.67 (m, 2H), 5.28 (s, 2H, CH_2PhF_2), 2.68 (s, 3H, CH_3). Anal. ($C_{25}H_{18}F_2N_2$) C,H,N.

EXAMPLE 30

Preparation Of 1-(2,6-Difluorobenzyl)-2-(2-Napthyl)-4-Methylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2-napthyl)-4-methylbenzimidazole (**38**) was produced according to Method C, using 2-(2-napthyl)-4-methylbenzimidazole (**22**) (0.30 g, 1.16 mmol) and 2,6-difluoro-α-bromo-toluene (**25**) (0.36 g, 1.74 mmol, 150 M%), and a second addition of 2,6-difluoro-α-bromo-toluene (0.18 g, 0.87 mmol, 75 M%) after 2 hours

of stirring. This mixture was stirred overnight, purified by flash chromatography, eluted with ethylacetate/hexane (1:4), and recrystallized from diethylether/hexane (3:1) to yield 0.35 g (0.91 mmol, 78% yield) of white powder, with a melting point of 175-176°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.28(d, J=1.6 Hz, 1H), 8.02 (d, J=8.5 Hz, 1H), 7.96 (m, 2H), 7.83 (dd, J=1.7, 8.5 Hz, 1H), 7.59 (m, 2H), 7.20(m, 2H), 7.12 (m, 1H), 7:06 (m, 1H), 6.80 (m, 2H), 5.60 (s, 2H, CH_2PhF_2), 2.66 (s, 3H, CH_3). Anal. ($C_{25}H_{18}F_2N_2$) C,H,N.

EXAMPLE 31

Preparation Of 1-(2,6-Difluorobenzyl)-2-Phenylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-phenylbenzimidazole (**39**) was produced according to Method C, using 2-phenylbenzimidazole (300 mg, 1.54 mmol) and 2,6-difluoro-α-bromo-toluene (**25**) (1.70 mmol, 110 M%). Recrystallization from diethylether:hexane (3:1) yielded 300 mg (0.94 mmol, 63% yield) of colorless crystals, with a melting point of 163°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.82 (d, J=8.3 Hz, 1H, H_4), 7.75 (m, 2H, $2H_{3',5'}$), 7.53 (m, 3H, $H_{2',4',6'}$), 7.33 (d, J=8.3 Hz, 1H, H_7), 7.25 (m, 3H, $H_{5,6,4''}$), 6.81 (m, 2H, $H_{3'',5''}$), 5.55 (s, 2H, CH_2). Anal. ($C_{20}H_{14}F_2N_2$x1/4H_2O)C,H,N.

EXAMPLE 32

Preparation Of 1-(2,6-Difluorobenzyl)-2-(3-Pyridyl)-4-Methylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(3-pyridyl)-4-methylbenzimidazole (**40**) was produced according to Method C, using 2-(3-pyridyl)-4-methylbenzimidazole (**23**) (0:30 g, 1.43 mmol) and 2,6-difluoro-α-bromo-toluene (**25**) (0.49 g, 2.37 mmol, 165 M%). After stirring overnight, purification by flash chromatography eluting with 4% MeOH/CH_2Cl_2, and recrystallization from diethylether/hexane (3:1) 0.34 g (1.02 mmol, 71% yield) of white powder was produced, with a melting point of 186-188°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.92 (dd, J=0.9, 2.3Hz, 1H, $H_{2''}$), 8.74 (dd, J=1.7, 4.9 Hz, 1H, H_6), 8.05 (dt, J=2.0, 7.8 Hz, 1H, $H_{4'}$), 7.48 (ddd, J=0.9, 4.9, 7.8, 1H, $H_{5'}$), 7.24 (m, 1H, $H_{4''}$), 7.22 (br d, J=7.7 Hz 1H, H_7), 7.15 (dd, J=7.7, 7.2, 1H, H_6), 7.07 (dt, J=1.0, 7.2 Hz 1H H_5), 6.83 (m, 2H, $H_{3'',5''}$), 5.51 (s, 2H, CH_2PhF_2), 2.64 (s, 3H, CH_3). Anal. ($C_{20}H_{15}F_2N_3$)C,H,N.

EXAMPLE 33

Preparation Of 1-(2,6-Difluorobenzyl)-2-(4-Pyridyl)-4-Methylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(4-pyridyl)-4-methylbenzimidazole (**41**) was produced according to Method C, using 2-(4-pyridyl)-4-methylbenzimidazole (**24**) (0.30 g, 1.43 mmol) and 2,6-difluoro-α-bromo-toluene (**25**) (0.45 g, 2.17 mmol, 150 M%). After stirring overnight, purification by flash chromatography eluting with 4% $MeOH/CH_2Cl_2$, and recrystallization from diethylether/hexane (3:1), 0.29 g (0.86 mmol, 60% yield) of white powder was produced with a melting point of 171-172°C. ^1H-NMR (300 MHz, CD_2Cl_2): δ 8.77 (dd, J=1.6, 4.4 Hz, 2H, $H_{2',6'}$), 7.66 (dt, J=1.4, 4.4 Hz, 2H, $H_{3',5'}$), 7.24 (m, 1H, $H_{4''}$), 7.22 (dd, J=0.8, 8.1 Hz, 1H, H_7), 7:15 (dd, J=7.5, 8.1 Hz, 1H, H_6), 7.07 (ddq, J=0.4, 0.8, 7.5 Hz, 1H, H_5), 6.82 (m, 2H, $H_{3'',5''}$), 5.54 (s, 2H, CH_2PhF_2), 2.63 (s, 3H, CH_3). Anal. ($C_{20}H_{15}F_2N_3$)C,H,N.

EXAMPLE 34

Preparation Of 1-(2,3,4,5,6-Pentafluorobenzyl)-2-(2,6-Difluorophenyl)-4-Methylbenzimidazole

In this Example, 1-(2,3,4,5,6-pentafluorobenzyl)-2-(2,6-difluorophenyl)-4-methylbenzimidazole (**42**) was prepared according to Method C, using 2-(2,6-difluorophenyl)-4-methylbenzimidazole (**19**) (0.31 g, 1.27 mmol) and 2,3,4,5,6-pentafluoro-α-bromo-toluene (0.30 mL, 1.99 mmol, 155 M%). After stirring for 4 hours, purification by flash chromatography, elution with 4% $MeOH/CH_2Cl_2$ and recrystallization from diethylether/hexane (3:1), 0.33 g (0.77 mmol, 61% yield) of white powder was produced, with a melting point of 155-156°C. ^1H-NMR (200 MHz, CD_2Cl_2); δ 7.57 (m, 1H, H_6), 7.29-7.23 (m, 2H, $H_{6,7}$), 7.19-7.05 (m, 3H, $H_{5,3',5'}$), 5.35 (s, 2H, CH_2PhF_5), 2.64 (s, 3H, CH_3). Anal. ($C_{21}H_{11}F_7N_2$)C,H,N.

EXAMPLE 35

Preparation Of 1-(3-Pyridylmethyl)-2-(2,6-Difluorophenyl)-4-Methylbenzimidazole

In this Example, 1-(3-pyridylmethyl)-2-(2,6-difluorophenyl)-4-methylbenzimidazole (**43**) was produced according to Method C, using 2-(2,6-difluorophenyl)-4-methylbenzimidazole (**19**) (0.21 g, 0.86 mmol) and α-bromo-methylpyridine (0.22 g, 1.28 mmol, 150 M%). After mixing for 1 hour, purification by flash chromatography eluting with ethylacetate/hexane (1:1) increasing to ethylacetate (100%), and recrystallization from diethyl ether/hexane (3:1), 0.24 g (0.73 mmol, 85% yield) of white powder was produced, with a melting point of 131-132°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.45 (d, J=3.4 Hz, 1H, $H_{6''}$), 8.32 (s, 1H, $H_{2''}$), 7.53 (m, 1H, $H_{4'}$), 7.25-7.03 (m, 7H, $H_{5,6,7,3',5',4'',5''}$), 5.26 (s, 2H, CH_2Py), 2.67 (s, 3H, CH_3-Ar). Anal. ($C_{20}H_{15}F_2N_3$x1/2H_2O)C,H,N.

EXAMPLE 36

Preparation of 1-(3,3-Dimethylallyl)-2-(Cyclopropyl)-4-Methoxylbenzimidazole

In this Example, 1-(3,3-dimethylallyl)-2-(cyclopropyl)-4-methoxylbenzimidazole was produced using Method C. To 2-amino-3-nitrophenol (**5001**) (2.00g, 12.98 mmol) dissolved in acetone (20 mL) was added K_2CO_3 (2.15 g), and methyl iodide (1.00 mL). After stirring overnight the reaction was concentrated, redissolved in ethylacetate, washed with water, $NaHSO_4$(10% solution), NaCl (sat. aq.), dried (Na_2SO_4), filtered, and concentrated. Flash chromatography eluting with (1:4) ethylacetate/hexane gave purified white crystals of 2-methoxyl-6-nitroaniline (**5002**) (1.79 g, 10.65 mmol, 82% yield): ^{1}H-NMR (300 MHz, CD_2Cl_2) δ 7.69 (dd, J = 1.4, 8.9 Hz, 1H, H_5), 6.92 (dd, J =1.4, 7.8 Hz, 1H, H_3), 6.62 (dd, J =8.9, 7.8 Hz, 1H, H_4), 6.42 (br, 2H, NH_2), 3.91 (s, 3H, OCH_3).

To 2-methoxyl-6-nitroaniline (**5002**) (4.15 g, 24.7 mmol) dissolved in THF:pyridine (1:1) (100 mL) was added cyclopropanecarbonyl chloride (2.7 mL, 29.8 mmol, 120 M%. After stirring at room temperature for 4 h, the reaction was concentrated to dryness and the residue was redissolved in CH_2Cl_2, washed with $NaHSO_4$ (10% solution), $NaHCO_3$ (sat. aq) and NaCl (sat. aq.), dried (Na_2SO_4), filtered and concentrated. Cyclopropanecarboxylic acid (2-methoxyl-6-nitro-phenyl)-amide (**5013**) was recrystallized from methanol (4.90 g, 20.8 mmol, 84% yield of white crystals): ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.82 (br, 1H, NH),

7.44 (dd. J= 1.6, 8.1 Hz. 1H. H_5), 7.25 (dd, J= 8.2. 8.1 Hz. 1H. H_4), 7.16 (dd. J= 1.7, 8.2 Hz, 1H, H_3), 3.95 (s, 3H. OCH_3), 1.65 (m, 1H), 0.94 (m, 4H).

Cyclopropanecarboxylic acid (2-methoxy-6-nitro-phenyl)-amide (**5013**) (7.80 g, 33.1 mmol) and iron powder (7.60 g) were suspended in acetic acid (200 mL) for 25 min at reflux. The reaction was concentrated and redissolved in ethyl acetate and washed with $NaHCO_3$ (sat. aq) and NaCl (sat. aq), dried (Na_2SO_4), filtered and concentrated and purified by flash chromatography with 2% MeOH/CH_2Cl_2 and recrystallization from diethyl ether/hexane (3:1) yielding white crystals of 2-(cyclopropyl)-4-methoxylbenzimidazole (**5014**) (4.90g, 26.1 mmol, 79% yield: ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.07 (cm, 2H), 6.65 (cm, 1H), 3.90 (s, 3H, OCH_3), 2.17-2.03 (m, 1H), 1.22-0.96 (m, 4H).

The compound 2-(cyclopropyl)-4-methoxylbenzimidazole (**5014**) (1.00 g, 5.32 mmol) and 3,3-dimethylallyl bromide (0.70 mL, 6.07 mmol, 115 M%) gave, after flash chromatography eluting with 2% MeOH/ CH_2Cl_2 and recrystallization from diethylether/hexane (3:1), 1.08 g (4.21 mmol, 80% yield) of white crystals: mp 41-42°C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.09 (dd, J= 8.1, 7.9 Hz, 1H, H_6), 6.89 (dd, J= 8.1, 0.9 Hz, 1H, H_5), 6.61 (dd, J = 7.9, 0.9 Hz, 1H, H_7), 5.26 (m, 1H), 4.81 (d, J=6.7 Hz, 2H), (3.94, s, 3H, OCH_3), 1.96 (m, 1H), 1.86 (s, 3H, CH_3), 1.74 (d, J=1.2 Hz, 3H, CH_3), 1.21-0.98 (m, 4H).

EXAMPLE 37

Preparation Of 1-Benzenesulfonyl-2-(2,6-Difluorophenyl)benzimidazole

In this Example, 1-benzenesulfonyl-2-(2,6-difluorophenyl)benzimidazole (**45**) was produced according to Method D. The benzimidazole compound **18** (0.31 g, 1.34 mmol) dissolved in THF (5 mL) was added to NaH (0.10 g, 190 M%). After 5 min, benzenesulfonyl chloride (**44**) (0.25 mL, 0.35 g, 2.00 mmol, 150 M%) was added. After stirring for 2 h, the reaction was dissolved in ethylacetate, washed with $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.), dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography eluting with 2% MeOH/CH_2Cl_2 and then recrystallized from diethylether/hexane (3:1), to yield (0.41 g, (1.10 mmol, 83% yield) of white powder, with a melting point of 104-106°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.09 (m, 1H, $PhSO_2$), 7.77 (m, 1H, $PhSO_2$), 7.69 (m, 2H, $PhSO_2$), 7.66-7.53 (m, 2H, $H_{4,7}$), 7.51-7.39 (m, 4H, $PhSO_2$, $H_{3,5}$), 7.07 (m, 2H, $H_{3',5'}$). Anal. ($C_{19}H_{12}F_2N_2SO_2$) C, H, N.

EXAMPLE 38

Preparation Of 1-Benzenesulfonyl-
2-(2,6-Difluorophenyl)-4-Methylbenzimidazole

In this Example, 1-benzenesulfonyl-2-(2,6-difluorophenyl)-4-methylbenzimidazole (**46**) was produced according to Method D, using 2-(2,6-difluorophenyl)-4-methylbenzimidazole (**19**) (0.20 g, 0.82 mmol) and benzenesulfonyl chloride (**44**) (0.20 mL, 0.28 g. 1.58 mmol, 190 M%), purified by flash chromatography eluting with 2% $MeOH/CH_2Cl_2$ and recrystallized from diethylether/hexane (3:1), to produce 0.24 g (0.02 mmol, 76% yield) of white powder, with a melting point of 134-135°C. ^{1}H-NMR (200 MHz, CD_2Cl_2): δ 7.89 (br d, J= 8.2 Hz, 1H), 7.73-7.38 (m, 6H), 7.34 (dd, J= 7.4, 8.1 Hz, 1H, H_6), 7.2 (br d, J= 7.4 Hz, 1H, H_5), 7.07 (m, 2H. $H_{3',5'}$), 2.59 (s, 3H, CH_3), Anal. ($C_{20}H_{14}F_2N_2SO_2$) C,H,N.

EXAMPLE 39

Preparation Of 1-(2,6-Difluorobenzoyl)-2-(2,6-Difluorophenyl)Benzimidazole

In this Example, 1-(2,6-difluorobenzoyl)-2-(2,6-difluorophenyl)benzimidazole (**47**) was produced according to Method D, using the benzimidazole compound **18** (30 mg, 0.13 mmol) dissolved in pyridine (0.5 mL) and chloroform (1.2 mL). To this mixture 2,6-difluorobenzoyl chloride (7) was added (20 μl, 0.16 mmol, 120 M%), and the mixture was stirred at room temperature for 5 h, diluted with chloroform, and washed with $NaHSO_4$ (2% solution). The organic layer was dried (Na_2SO_4), filtered, and evaporated. The solid was recrystallized from diethylether/hexane to produce 19 mg of colorless crystals (40% yield), with a melting point of 145°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.14 (m, 1H, H_4), 7.89 (m, 1H, H_7), 7.48 (m, 2H, $H_{5,6}$), 7.31-7.18 (m, 2H, $H_{4',4''}$), 6.77 (m, 4H, $H_{3',5',3'',5''}$). Anal. ($C_{20}H_{10}F_4N_2O$) C,H,N.

EXAMPLE 40

Preparation Of 1-(2,6-Difluorobenzyl)-
2-Hydroxymethyl-4-Methylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-hydroxymethyl-4-methylbenzimidazole (**48**) was prepared according to Method D, using 1-(2,6-difluorobenzyl)-2-*t*-butyldimethylsilyloxymethyl-4-methylbenzimidazole (**31**) (1.82 g, 4.52 mmol) dissolved in

THF (20mL). Tetrabutylammonium fluoride (1.45 g, 4.60 mmol, 100 M%) was then added. After 30 min at room temperature, the reaction was concentrated to dryness. The residue was suspended in water, filtered, and washed with water to produce 1.28 g, (4.44 mmol, 98% yield) of white powder. ^{1}H-NMR (300 MHZ, CD_3OD): δ 7.39(m, 1H, $H_{4'}$), 7.18 (br d, J= 8.3 Hz, 1H, H_7), 7.09 (dd, J= 7.4, 8.3 Hz, 1H, H_6), 7.05-6.97 (m, 3H, $H_{3'',5'',5}$), 5.68 (s, 2H, CH_2PhF_2), 4.99 (s, 2H, CH_2O), 2.57 (s, 3H, CH_3). Anal. ($C_{16}H_{14}F_2N_2O$) C,H,N.

EXAMPLE 41

Preparation Of 1-(2,6-Difluorobenzyl)-4-Methylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-4-methylbenzimidazole (**49**) was prepared according to Method D, using 1-(2,6-difluorobenzyl)-2-hydroxymethyl-4-methylbenzimidazole (**48**) (1.82 g, 4.52 mmol) dissolved in 1.5 M H_2SO_4 (40 mL). $KMnO_4$ (1.50 g, 9.49 mmol, 160 M%) was then added. After 1 h at room temperature, the reaction mixture was filtered and washed with water. The brown solid was collected, suspended in acetone/methanol and filtered. The filtrate was collected and purified by flash chromatography eluting with 10% $MeOH/CH_2Cl_2$ increasing to 50% $MeOH/CH_2Cl_2$ to produce 1.42 g (4.70 mmol, 80% yield) of white powder. ^{1}H-NMR (200 MHz, CD_2Cl_2): δ 7.99 (br s, 1H, H_2), 7.37 (br d , J= 7.9 Hz, 1H, H_7), 7.32 (m, 1H, $H_{4''}$), 7.17 (dd, J= 7.3, 7.9 Hz, 1H, H_6), 7.03 (d, J= 7.3 Hz, 1H, H_5), 6.96 (m, 2H, $H_{3'',5''}$), 5.40 (s, 2H, CH_2PhF_2), 2.59 (s, 3H, CH_3), Anal. ($C_{15}H_{12}F_2N_2$ x $1/4H_2O$) C,H,N.

EXAMPLE 42

Preparation Of 1-(2,6-Difluorobenzyl)-2-Formyl-4-Methylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-formyl-4-methylbenzimidazole (**50**) was prepared according to Method D. Pyridine (3.4 mL) dissolved in CH_2Cl_2 (50 mL) was added to CrO_3 (2.20 g). After 15 min., 1-(2,6-difluorobenzyl)-2-hydroxymethyl-4-methylbenzimidazole (**48**) dissolved in DMF was added to the mixture and stirred. After 20 m, the organic solution was decanted from a tarry black deposit. The organic solution was washed with 5% NaOH, 5% HCl, $NaHCO_3$ and NaCl, dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography eluting with 2% $MeOH/CH_2Cl_2$ gave 0.55 g (1.92 mmol, 44% yield) of 1-(2,6-difluorobenzyl)-2-formyl-4-methylbenzimidazole (**50**) and

0.17 g (0.66 mmol, 15% yield) of 1-(2,6-difluorobenzyl)-4-methylbenzimidazole (**49**). ^{1}H-NMR (200 MHz, CD_3OD): δ 10.13 (s, 1H, CHO), 7.36-7.10 (cm, 4H, $H_{5,6,7,4''}$), 6.90 (m, 2H, $H_{3',5'}$), 6.05 (s, 2H, Ch_2PhF_2), 2.66 (s, 3H, CH_3). Anal. ($C_{16}H_{12}F_2N_2O$x1/5H_2O)C,H,N.

EXAMPLE 43

Preparation of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-4-cyanobenzimidazole (**4007**)

Examples 43-48 provide 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole compositions with general structure of Figure 24.

In this example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-cyanobenzimidazole (**4007**) was prepared in five steps from methyl *N,N*-bis(2,6-difluorobenzoyl)-6-nitro-2-anilidecarboxylate (4002). To methyl 2-amino-6-nitrobenzoate (**4001**) (12.75 g, 65.0 mmol) dissolved in THF:pyridine (1:1) (300 mL) was added 2,6-difluorobenzoyl chloride (18.0 mL, 142.7 mmol, 220 M%). After a second addition at 7 h of 2,6-difluorobenzoyl chloride (8.0 mL, 64 mmol, 100 M%) and stirring overnight at room temperature, the reaction was concentrated. The residue was suspended in water and filtered. The filtrate was then suspended in boiling methanol and filtered yielding methyl *N,N*-bis(2,6-difluorobenzoyl)-6-nitro-2-anilidecarboxylate (**4002**) (28.26 g, 59.3 mmol, 91% yield): ^{1}H-NMR (200 MHz, DMSO-d_6) δ 8.41 (dd, J= 1.5, 8.2 Hz, 1H, H_5), 8.29 (dd, J= 1.5, 8.0 Hz, 1H, H_3), 7.86 (dd, J= 8.0, 8.2 Hz, 1H, H_4), 7.55 (m, 2H, $H_{4',4'}$), 7.13 (m, 4H, $H_{3',5',3',5'}$), 3.86 (s, 3H, CO_2Me).

To methyl *N,N*-bis(2,6-difluorobenzoyl)-6-nitro-2-anilidecarboxylate (**4002**) (28.20 g, 59.2 mmol) suspended in pyridine (300 mL) was added hydrazine (3.0 mL, 61.7 mmol, 105 M%). After 6 h at room temperature, the reaction was concentrated and the residue was redissolved in CH_2Cl_2, washed with $NaHCO_3$ (sat. aq.), and NaCl (sat. aq.), dried (Na_2SO_4), filtered, evaporated, and recrystallized from MeOH yielding methyl *N*-(2,6-difluorobenzoyl)-6-nitro-2-anilidecarboxylate (**4003**) (18.31 g, 54.5 mmol, 92% yield): ^{1}H-NMR (200 MHz,CD_2Cl_2) δ 10.81 (br, 1H, NH), 8.22 (dd, J= 1.7, 8.1 Hz, 1H, H_5), 8.15 (dd, J= 1.7, 8.1 Hz, 1H, H_3), 7.50 (m, 1H, $H_{4'}$), 7.42 (dd, J= 8.1, 8.1 Hz, 1H, H_4), 7.05 (m, 2H, $H_{3',5'}$), 3.94 (s, 3H, CO_2Me).

Methyl *N*-(2,6-difluorobenzoyl)-6-nitro-2-anilidecarboxylate (**4003**) (19.33 g, 57.5 mmol) and iron powder (19.3 g) gave, after 1 h and recrystallization from MeOH, methyl 2-

(2,6-difluorophenyl)benzimidazole-2-carboxylate (**4004**). (14.67 g, 50.9 mmol, 89% yield) of white solid: ^{1}H-NMR (300 MHz, CD_2Cl_2) δ 10.92 (br, 1H, NH), 8.06 (d, J=8.1 Hz,1H, H_5), 7.97 (1H, dd, J= 1.0, 7.6 Hz, 1H, H_7), 7.49 (m, 1H, $H_{4'}$), 7.37 (dd, J= 8.1, 7.6 Hz, 1H, H_6), 7.14 (m, 2H, $H_{3',5'}$), 4.01 (s, 3H, CH_3).

Methyl 2-(2,6-difluorophenyl)benzimidazole-2-carboxylate (**4004**) (16.15 g, 56.0 mmol) and 2,6-difluoro-α-bromo-toluene (14.67 g, 70.86 mmol, 125 M%) gave after flash chromatography eluting with 2% MeOH/CH_2Cl_2 and recrystallization from diethylether, white crystals of methyl 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole-2-carboxylate (**4005**) (17.63 g, 42.55 mmol, 76 % yield, with mp 185-186°C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.94 (dd, J= 1.1, 7.6 Hz, 1H, H_5), 7.72 (dd, J= 1.1, 8.2 Hz, 1H, H_7), 7.56 (m, 1H, $H_{4'}$), 7.37 (dd, J= 7.6, 8.2 Hz, 1H, H_6), 7.26 (m, 1H, $H_{4''}$), 7.09 (m, 2H, $H_{3',5'}$), 6.82 (m, 2H, $H_{3'',5''}$), 5.39 (s, 2H, CH_2PhF_2), 3.95 (s, 3H, CO_2CH_3).

To methyl 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole-2-carboxylate (**4005**) (1.02 g, 2.46 mmol) dissolved in methanol (20 mL) was added barium hydroxide (1.20 g). After 2 h, acetic acid was added and the reaction concentrated. The residue was redissolved in CH_2Cl_2 and washed with $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.), dried (Na_2SO_4), filtered and concentrated. The product was purified by flash chromatography eluting with 8% MeOH/ CH_2Cl_2 and recrystallization from diethylether/ hexane (3:1) gave 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole-2-carboxylate (**4006**) (0.71 g, 1.77 mmol, 72 % yield) of white crystals with mp 179-180°C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 8.06 (d, J= 7.8 Hz, 1H, H_5), 7.76 (d, J= 8.1 Hz, 1H, H_7), 7.62 (m, 1H, $H_{4'}$), 7.47 (dd, J= 7.8, 8.1 Hz, 1H, H_6), 7.29 (m, 1H, $H_{4''}$), 7.14 (m, 2H, $H_{3',5'}$), 6.85 (m, 2H, $H_{3'',5''}$), 5.45 (s, 2H, CH_2PhF_2).

To methyl 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole-2-carboxylate (**4006**) (2.00 g, 4.83 mmol) suspended in xylene (50 mL) was added a freshly prepared 1.0 M solution of $AlMe_2NH_2$ (7 mL, 7.00 mmol, 145 M%). After 45 min at reflux, the reaction was concentrated and then redissolved in CH_2Cl_2. The organic solution was washed with $NaHSO_4$ (10% solution) (add slowly!), $NaHCO_3$ (sat. aq) and NaCl (sat. aq), dried (Na_2SO_4), filtered and concentrated. The product was purified by flash chromatography eluting with 1% methanol/ CH_2Cl_2 and recrystallization from diethylether, to produce white crystals of 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-cyanobenzimidazole (**4007**) (1.50 g, 3.93 mmol, 81 % yield) with mp 153-155°C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.76 (dd, J= 1.1, 8.6 Hz, 1H,

H_5), 7.63 (dd, J= 1.0, 7.6 Hz, 1H, H_7), 7.58 (m, 1H, $H_{4'}$), 7.37 (dd, J= 7.6, 8.6 Hz, 1H, H_6), 7.28 (m, 1H, $H_{4''}$), 7.11(m, 2H, $H_{3',5'}$), 6.83 (m, 2H, $H_{3'',5''}$), 5.40 (s, 2H, CH_2PhF_2).

EXAMPLE 44

Preparation of 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-(propan-2-ol)benzimidazole (**4015**)

To methyl 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole-2-carboxylate (1.00 g, 2.41 mmol) dissolved in THF (20 mL) was added 3M methyl magnesium bromide (3.00 mL, 9.00 mmol). After 1 h, the reaction was concentrated and the residue was redissolved in CH_2Cl_2 and washed with $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.), dried (Na_2SO_4), filtered and concentrated. The product was purified by flash chromatography eluting with 2% MeOH/CH_2Cl_2 and recrystallization from diethylether/hexane (3:1) gave 0.95 g (2.29 mmol, 95% yield) of white crystals: mp 149-150 °C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.55 (m, 1H, H4'), 7.40 (d, J= 8.1 Hz, 1H, H_5), 7.25 (m, 2H, $H_{4'',6}$), 7.16 (dd, J= 1.1, 7.6 Hz, 1H, H_7), 7.10 (m, 2H, $H_{3',5'}$), 6.82 (m, 2H, $H_{3'',5''}$), 5.82 (s, 1H, OH), 5.37 (s, 2H, CH_2PhF_2), 1.67 (s, 6H, iPr).

EXAMPLE 45

Preparation of 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-(isopropenyl)benzimidazole (**4016**)

To concentrated H_2SO_4 (1.00 mL) at room temperature was added 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-(propan-2-ol)benzimidazole (**4015**) (0.45 g, 1.09 mmol). After 15 min, the reaction was diluted with ethylacetate. The organic solution was washed with $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.), dried (Na_2SO_4), filtered and concentrated. The product was purified by flash chromatography eluting with 1% MeOH/CH_2Cl_2 and recrystallization from diethylether/ hexane (3:1) to produce 0.11 g (0.28 mmol, 30 % yield) of white crystals with mp 156-158°C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.53 (m, 1H, $H_{4'}$), 7.44-16 (m, 4H, $H_{4'',5,6,7}$), 7.07 (m, 2H, $H_{3',5'}$), 6.81 (m, 2H, $H_{3'',5''}$), 6.03 (dq, J= 0.9, 2.4 Hz, 1H, vinyl), 5.36 (dq, J= 1.5, 2.4 Hz, 1H, vinyl), 5.35 (s, 2H, CH_2PhF_2), 2.33 (dd, J= 0.8, 1.5 Hz, 3H, CH_3).

EXAMPLE 46

Preparation of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-4-methoxylbenzimidazole (5006)

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-methoxylbenzimidazole (**5006**) was prepared in four steps from 2-methoxyl-6-nitroaniline (**5002**). To 2-amino-3-nitrophenol (**5001**) (2.00g, 12.98 mmol) dissolved in acetone (20 mL) was added K_2CO_3 (2.15 g), and methyl iodide (1.00 mL). After stirring overnight the reaction was concentrated, redissolved in ethylacetate, washed with water, $NaHSO_4$(10% solution), NaCl (sat. aq.), dried (Na_2SO_4), filtered, and concentrated. Flash chromatography eluting with (1:4) ethylacetate/hexane gave purified white crystals of 2-methoxyl-6-nitroaniline (**5002**) (1.79 g, 10.65 mmol, 82% yield): ^{1}H-NMR (300 MHz, CD_2Cl_2) δ 7.69 (dd, J = 1.4, 8.9 Hz, 1H, H_5), 6.92 (dd, J =1.4, 7.8 Hz, 1H, H_3), 6.62 (dd, J =8.9, 7.8 Hz, 1H, H_4), 6.42 (br, 2H, NH_2), 3.91 (s, 3H, OCH_3).

To 2-methoxyl-6-nitroaniline (**5002**) (13.75 g, 81.8 mmol) dissolved in THF:pyridine (1:1) (300 mL) was added 2,6-difluorobenzoyl chloride (**4**) (22.0 mL, 174.4 mmol, 215 M%. After stirring overnight at room temperature, the reaction was concentrated to dryness and the residue was redissolved in CH_2Cl_2, washed with $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.), dried (Na_2SO_4), filtered and concentrated. The product was recrystallized from methanol to give white crystals of *N,N*-Bis-(2,6-difluorobenzoyl)-2-methoxyl-6-nitroanilide (**5003**) (33.7 g, 75.2 mmol. 92% yield): ^{1}H-NMR (300 MHz, CD_2Cl_2) δ 7.70 (dd, J= 1.4, 8.4 Hz, 1H, H_5), 7.48 (dd, J= 8.4, 8.4 Hz, 1H, H_4), 7.35 (2H, m, $H_{4',4'}$), 7.15 (dd, J= 1.4, 8.4 Hz, 1H, H_3), 6.87 (m, 4H, $H_{3',5',3',5'}$), 3.85 (s, 3H, OCH_3).

N,N-bis-(2,6-difluorobenzoyl)-2-methoxyl-6-nitroanilide (**5003**) (33.7 g, 75.2 mmol) dissolved in pyridine (500 mL) was added hydrazine (4.50 mL, 92.6 mmol, 120 M%). After stirring overnight at room temperature, the reaction was concentrated and the residue was redissolved in CH_2Cl_2, washed with $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.), dried (Na_2SO_4), filtered. evaporated, and recrystallized from methanol yielding white solids of *N*-(2,6-difluorobenzoyl)-2-methoxyl-6-nitroanilide (**5004**) (22.39 g, 72.6 mmol, 96% yield): ^{1}H-NMR (200 MHz,CD_2Cl_2). δ 8.82 (br, 1H, NH), 7.51 (dd, J= 1.6, 8.1 Hz, 1H, H_5), 7.45 (m, 1H, $H_{4'}$), 7.35 (dd, J= 8.2, 8.3 Hz, 1H, H_4), 7.12 (dd, J= 8.3, 1.6 Hz, 1H, H_3), 7.01 (m, 2H, $H_{3',5'}$), 3.92 (s, 3H, OMe).

N-(2,6-difluorobenzoyl)-2-methoxyl-6-nitroanilide (**5004**) (2.20 g, 7.15 mmol) and iron powder (2.20 g) gave, after 1 h and flash chromatography with 2% MeOH/CH_2Cl_2, white crystals of 2-(2,6-difluorophenyl)-4-methoxylbenzimidazole (**5005**) (1.68 g, 6.18 mmol, 86% yield): ^{1}H-NMR (300 MHz, CD_2Cl_2) δ 10.07 (br d, J= 36 Hz, 1H, NH), 7.40 (cm, 1H), 7.29-7.00 (cm, 4H), 6.75 (dd, J= 8.0, 13.8 Hz, 1H), 4.00 (d, J= 4.2 Hz, 3H, OCH_3).

2-(2,6-Difluorophenyl)-4-methoxylbenzimidazole (**5005**) (1.25 g, 4.80 mmol) and 2,6-difluoro-α-bromo-toluene (1.30 g, 6.28 mmol, 130 M%) gave after flash chromatography eluting with 2% MeOH/CH_2Cl_2 and recrystallization from diethylether/hexane (3:1), white crystals of 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-methoxylbenzimidazole (**5006**) (1.68g, 4.35 mmol, 91% yield) with mp 154-155°C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.52 (m, 1H, $H_{4'}$), 7.25 (m, 1H, $H_{4''}$), 7.19 (dd, J = 7.8, 1.0 Hz, 1H, H_5), 7.13-7.00 (m, 3H, $H_{3',5',6}$), 6.81 (m, 2H, $H_{3'',5''}$), 6.72 (dd, J = 7.8, 1.0 Hz, H_7), 5.33 (s, 2H, CH_2PhF_2), 4.00 (s, 3H, OCH_3). Anal. ($C_{21}H_{14}F_4N_2O$) C, H, N.

EXAMPLE 47

Preparation of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-4-ethylbenzimidazole (4011)

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-ethylbenzimidazole (**4011**) was prepared in two steps from *N*-(2,6-difluorobenzoyl)-2-ethyl-6-nitroanilide (**4009**). 2-Ethyl-6-nitroaniline (**4008**) (3.10 g, 18.65 mmol) and 2,6-difluorobenzoyl chloride (3.50 mL, 27.83 mmol, 150 M%) gave, after stirring overnight at room temperature and flash chromatography with 2% MeOH/CH_2Cl_2 and recrystallization from ethylacetate/hexane (1:4), *N*-(2,6-difluorobenzoyl)-2-ethyl-6-nitroanilide (2.34 g, 7.64 mmol, 41% yield): ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 8.25 (br, 1H, NH), 7.85 (dd, J = 1.7, 8.1 Hz, 1H, H_5), 7.66 (dd, J = 1.7, 7.9 Hz, 1H, H_3), 7.49 (m, 1H, $H_{4'}$), 7.45 (dd, J = 7.9, 8.1 Hz, 1H, H_4), 7.06 (m, 2H, $H_{3',5'}$), 2.81 (q, J =7.6 Hz, 2H, CH_2), 1.29 (t, J =7.6 Hz, 3H, CH_3).

N-(2,6-Difluorobenzoyl)-2-ethyl-6-nitroanilide (**4009**) (2.00 g, 6.53 mmol) and iron powder (2.00 g) gave, after 0.5 h at room temperature, flash chromatography with 2% MeOH/CH_2Cl_2, and recrystallization from CH_2Cl_2, white crystals of 2-(2,6-difluorophenyl)-4-ethylbenzimidazole (**4010**) (1.65 g, 6.39 mmol, 98% yield): ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 9.78 (br, 1H, NH), 7.46 (br, 1H, H_5), 7.45 (m, 1H, $H_{4'}$), 7.23 (dd, J = 7.4, 7.9 Hz, 1H, H_6), 7.17-7.04 (m, 3H, $H_{3',5',7}$), 3.03 (br, 2H, CH_2), 1.39 (t, J = 7.7 Hz, 3H, CH_3).

2-(2,6-Difluorophenyl)-4-ethylbenzimidazole (**4010**) (0.70 g, 2.71 mmol) and 2,6-difluoro-α-bromo-toluene (0.72 g, 3.48 mmol, 130 M%) gave, after flash chromatography eluting with 2% MeOH/CH_2Cl_2 and recrystallization from diethylether/hexane (3:1), white crystals of 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-ethylbenzimidazole (**4011**) (0.79 g, 2.06 mmol, 76% yield) with mp 165-166°C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.53 (m, 1H, $H_{4'}$), 7.32 (d, J = 8.2 Hz, 1H, H_5), 7.29-7.16 (m, 2H, $H_{6,4''}$), 7.14-7.01 (m, 1H, H_7), 7.07 (m, 2H, $H_{3',5'}$), 6.81 (m, 2H, $H_{3'',5''}$), 5.33 (s, 2H, CH_2), 3.07 (q, J =7.6 Hz, 2H, CH_2), 1.35 (t, J = 7.6 Hz, 3H, CH_3). Anal. ($C_{22}H_{16}F_4N_2$) C, H, N.

EXAMPLE 48

Preparation of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-4-(*N*-methylamino)benzimidazole (**4006**)

First, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-(*N*-methylacetamido)benzimidazole (**4005**) was prepared. To 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-(*N*-acetamido)benzimidazole (2.44 g, 5.90 mmol) and methyl iodide (0.60 mL, 9.69 mmol) dissolved in THF (30 mL) was added excess NaH. After stirring overnight, the solution was concentrated to dryness, diluted with CH_2Cl_2, washed with water, $NaHSO_4$ (10% solution) and NaCl (sat. aq.), dried (Na_2SO_4), filtered, concentrated and purified by flash chromatography eluting with 2% methanol in CH_2Cl_2 to give 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-(*N*-methylacetamido)benzimidazole (0.89 g, 2.08 mmol, 63% yield, and 1.07 g recovered starting material): mp 155-156°C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.55 (m, 1H, $H_{4'}$), 7.48 (br d, J =7.4 Hz, 1H, H_5), 7.31 (dd, J = 7.4, 7.7 Hz, 1H, H_6), 7.27 (m, 1H, $H_{4''}$), 7.14 (dd , J = 1.1, 7.7 Hz, 1H, H_7), 7.09 (m, 2H, $H_{3',5'}$), 6.84 (m, 2H, $H_{3'',5''}$), 5.38 (s, 2H, CH_2PhF_2), 3.34 (s, 3H, NCH_3), 1.83 (s, 3H, NAc). Anal. ($C_{23}H_{17}F_4N_3O$) C, H, N.

To 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-(*N*-methylacetamido)benzimidazole (**4005**) (0.50 g, 1.17 mmol) suspended in water (9.0 mL) was added HCl (1.0 mL). After 3 h at reflux, the solution was concentrated to dryness, diluted with ethylacetate, washed with $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.), dried (Na_2SO_4), filtered, concentrated and purified by flash chromatography eluting with 2% methanol in CH_2Cl_2 gave 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-(*N*-methylamino)benzimidazole (**4006**) (0.35 g, 78 % yield): mp 194-195°C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.52 (m, 1H, $H_{4'}$), 7.23 (m, 1H, $H_{4''}$), 7.13 (dd, J = 8.3, 8.0 Hz, 1H, H_6), 7.07 (m, 2H, $H_{3',5'}$), 6.80 (m, 2H, $H_{3'',5''}$), 6.76 (d, J = 8.3 Hz, 1H, H_5),

6.36 (d, J = 8.0 Hz, 1H, H_7), 5.29 (s, 2H, CH_2PhF_2), 2.96 (s, 3H, NCH_3). Anal. ($C_{21}H_{15}F_4N_3$) C, H, N.

EXAMPLE 49

Preparation of 1-(2,6-Difluorobenzyl)-2-(Cyclopropyl)-4-Methoxylbenzimidazole (**5016**)

Examples 49-50 provide 1-(2,6-difluorobenzyl)-benzimidazole compositions with general structure of Figure 13.

In this Example, 1-(2,6-difluorobenzyl)-2-(cyclopropyl)-4-methoxylbenzimidazole (**5016**) was prepared in two steps from cyclopropanecarboxylic acid (2-methoxy-6-nitro-phenyl)-amide (**5013**). To 2-methoxyl-6-nitroaniline (**5002**) (4.15 g, 24.7 mmol) dissolved in THF:pyridine (1:1) (100 mL) was added cyclopropanecarbonyl chloride (2.7 mL. 29.8 mmol. 120 M%. After stirring at room temperature for 4 h, the reaction was concentrated to dryness and the residue was redissolved in CH_2Cl_2, washed with $NaHSO_4$ (10% solution), $NaHCO_3$ (sat. aq) and NaCl (sat. aq.), dried (Na_2SO_4), filtered and concentrated. Cyclopropanecarboxylic acid (2-methoxyl-6-nitro-phenyl)-amide (**5013**) was recrystallized from methanol (4.90 g, 20.8 mmol, 84% yield of white crystals): ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.82 (br, 1H, NH), 7.44 (dd, J= 1.6, 8.1 Hz, 1H, H_5), 7.25 (dd, J= 8.2, 8.1 Hz, 1H, H_4), 7.16 (dd, J= 1.7, 8.2 Hz, 1H, H_3), 3.95 (s, 3H, OCH_3), 1.65 (m, 1H), 0.94 (m, 4H).

Cyclopropanecarboxylic acid (2-methoxy-6-nitro-phenyl)-amide (**5013**) (7.80 g, 33.1 mmol) and iron powder (7.60 g) were suspended in acetic acid (200 mL) for 25 min at reflux. The reaction was concentrated and redissolved in ethyl acetate and washed with $NaHCO_3$ (sat. aq) and NaCl (sat. aq), dried (Na_2SO_4), filtered and concentrated and purified by flash chromatography with 2% MeOH/CH_2Cl_2 and recrystallization from diethyl ether/hexane (3:1) yielding white crystals of 2-(cyclopropyl)-4-methoxylbenzimidazole (**5014**) (4.90g, 26.1 mmol, 79% yield: ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.07 (cm, 2H), 6.65 (cm, 1H), 3.90 (s, 3H, OCH_3), 2.17-2.03 (m, 1H), 1.22-0.96 (m, 4H).

2-(Cyclopropyl)-4-methoxylbenzimidazole (1.00 g, 5.32 mmol) (**5014**) and 2,6-difluoro-α-bromo-toluene (1.30 g, 6.28 mmol, 130 M%) gave after flash chromatography eluting with 2% methanol/ CH_2Cl_2 and recrystallization from diethylether/hexane (3:1), white crystals of 1-(2,6-difluorobenzyl)-2-(cyclopropyl)-4-methoxylbenzimidazole (**5016**) (1.54 g, 4.90 mmol, 92% yield) with mp 136-139°C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.31 (m, 1H.

$H_{4'}$), 7.07 (dd, J= 8.0, 7.8 Hz, 1H, H_6), 6.94 (m, 3H, $H_{3',5',5}$), 6.61 (dd, J = 7.8, 1.0 Hz, H_7), 5.46 (s. 2H, CH_2PhF_2), 3.95 (s, 3H, OCH_3), 2.20-2.03 (m, 1H), 1.18-0.97 (m, 4H).

EXAMPLE 50

Preparation of 1-(2,6-Difluorobenzyl)-2-(2-Fluoro-6-Methoxylphenyl)-4-Nitrobenzimidazole (**5008**)

To 2-(2-fluoro-6-methoxylphenyl)-4-nitrobenzimidazole (2.00 g, 8 mmol) and 2,6-difluoro-α-bromo-toluene (2.02 g, 9.76 mmol, 130 M%) dissolved in THF (20 mL) was added NaH (0.84 g, 21 mmol, 290 M%). After 8 h, the reaction was quenched with methanol and concentrated. The residue was dissolved in CH_2Cl_2, washed with water and NaCl (sat. aq.), dried (Na_2SO_4), filtered, concentrated and purified by flash chromatography eluting with ethylacetate/hexane (1:1) (2.33 g, 5.64 mmol, 78%): mp 189-192°C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 8.11 (dd, J = 8.1, 1.0 Hz, 1H, H_5), 7.84 (dd, J = 8.1, 1.0 Hz, 1H, H_7), 7.52 (m, 1H, $H_{4'}$), 7.40 (dd, J = 8.1 Hz, 1H, H_6), 7.26 (m, 1H, $H_{4''}$), 6.89-6.74 (m, 4H, $H_{3',5',3'',5''}$), 5.36 (d, J =3.4Hz, 2H, CH_2PhF_2 (rotamers)), 3.73 (s, 3H, OCH_3). Anal. ($C_{21}H_{14}F_3N_3O_3$) C, H, N.

EXAMPLE 51

Preparation of 1-(2,6-Difluorobenzyl)-2-(2-Fluoro-6-Methoxylphenyl)-4-Aminobenzimidazole (**5009**)

To 1-(2,6-difluorobenzyl)-2-(2-fluoro-6-methoxylphenyl)-4-nitrobenzimidazole (**5008**) (2.00 g, 4.98 mmol) dissolved in acetic acid (20 mL) was added $SnCl_2x2H_2O$ (9.02 g) dissolved in concentrated HCl (8 mL). After stirring for 30 min at room temperature, the mixture was concentrated. The residue was diluted with CH_2Cl_2 and washed with $NaHCO_3$ (sat. aq.), and NaCl (sat. aq.), dried (Na_2SO_4), filtered, evaporated, and recrystallized from methanol to give 3.26 g of white crystals, (8.78 mmol, 70% yield): mp 200-202°C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.45 (m, 1H, $H_{4'}$), 7.22 (m, 1H, $H_{4''}$), 7.05 (dd, J = 7.8, 7.6 Hz, 1H, H_6), 6.85-6.72 (m, 5H, $H_{3'',5''}$), 6.50 (dd, J = 7.7, 1.0 Hz, 1H, H_5), 5.21 (d, J =5.4 Hz, 2H, CH_2PhF_2 (rotamers)), 4.34 (br, 2H, NH_2), 3.72 (s, 3H, OCH_3). Anal. ($C_{21}H_{16}F_3N_3O$) C, H, N.

EXAMPLE 52

Preparation of 1-Benzyl-2-(2,6-Difluorophenyl)-4-Methoxylbenzimidazole (**5007**)

Examples 52-57 provide 2-(2,6-difluorobenzyl)benzimidazole compositions with general structure of Figure 12.

2-(2,6-Difluorophenyl)-4-methoxylbenzimidazole (**5005**) (2.02 g, 7.77 mmol) and benzyl bromide (1.20 mL, 10.1 mmol, 130 M%) gave after flash chromatography eluting with 2% MeOH/ CH_2Cl_2 and recrystallization from diethylether/hexane (3:1) 2.47 g (7.05 mmol, 90 % yield) of white crystals with mp 139-141°C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.48 (m, 1H, $H_{4'}$), 7.25-6.96 (m, 8H), 6.86 (dd, J = 0.8, 8.3 Hz, 1H, H_5), 6.72 (dd, J= 8.0, 0.8 Hz, 1H, H_7), 5.24 (s. 2H. CH_2Ph), 4.01 (s, 3H, OCH_3).

EXAMPLE 53

Preparation of 1-(Ethylbenzyl)-2-(2,6-Difluorophenyl)-
4-methoxylbenzimidazole (**5008**)

2-(2,6-Difluorophenyl)-4-methoxylbenzimidazole (**5005**) (0.10 g, 0.38 mmol) and (1-bromoethyl)benzene (0.28 mL) gave after flash chromatography eluting with 2% MeOH/ CH_2Cl_2 and recrystallization from diethylether/hexane (3:1) 0.12 g (0.33 mmol, 86 % yield) of white crystals: mp 139-141°C; ^{1}H-NMR (200 MHz, CD_2Cl_2) δ 7.51 (m, 1H, $H_{4'}$), 7.25 (dd, J= 8.0, 8.1 Hz, 1H, H_6), 7.17 (m, 3H, Ph), 7.06 (m, 2H, $H_{3',5'}$), 7.04 (dd, J= 8.1, 0.8 Hz, 1H, H_5), 6.91 (m, 2H, Ph), 6.74 (dd, J = 0.8, 8.0 Hz, H_7), 4.27 (t, J= 7.5 Hz, 2H), 4.03 (s, 3H, OCH_3), 3.00 (t, J= 7.5 Hz, CH_2Ph).

EXAMPLE 54

Preparation of 1-(3,3-Dimethylallyl)-2-(2,6-Difluorophenyl)-4-Methoxylbenzimidazole (**5009**)

To 2-(2,6-difluorophenyl)-4-methoxylbenzimidazole (**5005**) (0.28 g, 1.08 mmol) and 3,3-dimethylallyl bromide (0.20 mL, 0.26 mmol, 160 M%) dissolved in THF (3 mL) was added NaH (60% dispersion in mineral oil) (0.15 g, 3.75 mmol, 350 M%). After 4 h, the

reaction was quenched with MeOH and concentrated. The residue was redissolved in dichloromethane, washed with water and NaCl (sat. aq.), dried (Na_2SO_4), filtered and concentrated. The product was purified by flash chromatography eluting with 2% MeOH/CH_2Cl_2 and recrystallized from hexane (0.30 g, 0.91 mmol, 84% yield of white powder): mp 101-103 °C; ^{1}H-NMR (200 MHz, CD_2Cl_2): 7.52 (m, 1H, $H_{4''}$), 7.24 (dd, J= 7.9, 8.2 Hz, 1H, H_6), 7.08 (m, 2H, $H_{3'',5''}$), 7.02 (dd, J= 0.9 , 8.2 Hz, 1H, H_5), 6.73 (dd, J= 0.9, 7.9 Hz, 1H, H_7), 5.19 (t, J= 7.0 Hz, 1H, $H_{2'}$), 4.02 (s, 3H, OCH_3), 4.62 (d, J= 7.0 Hz, 2H, $H_{1'}$), 1.64 (s, 3H, CH_3), 1.58 (s, 3H, CH_3). Anal. ($C_{19}H_{18}F_2N_2O$) C,H,N.

EXAMPLE 55

Preparation of 1-(3,3-Dimethylallyl)-2-(2,6-difluorophenyl)-4-methylbenzimidazole **(6003)**

To 2-(2,6-difluorophenyl)-4-methylbenzimidazole (**6002**) (0.50 g, 2.05 mmol) and 3,3-dimethylallyl bromide (0.50 mL, 4.34 mmol, 210 M%) dissolved in THF (10 mL) was added NaH (60% dispersion in mineral oil) (0.17 g, 4.25 mmol, 200 M%). After 4 h, the reaction was quenched with MeOH and concentrated. The residue was redissolved in dichloromethane, washed with water and NaCl (sat. aq.), dried (Na_2SO_4), filtered and concentrated. The product was purified by flash chromatography eluting with 2% MeOH/CH_2Cl_2 and recrystallized from hexane (0.40 g, 1.28 mmol, 63% yield of white powder): mp 78-79 °C; ^{1}H-NMR (200 MHz, CD_2Cl_2): 7.52 (m, 1H, $H_{4''}$), 7.26-7.02 (m, 5H, $H_{5,6,7,3'',5''}$), 5.18 (t, J= 6.8 Hz, 1H, $H_{2'}$), 4.62 (d, J= 6.8 Hz, 2H, $H_{1'}$), 2.64 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.57 (s, 3H, CH_3). Anal. ($C_{19}H_{18}F_2N_2$) C,H,N.

EXAMPLE 56

Preparation of 1-(3,3-Dimethylallyl)-2-(2,6-difluorophenyl)-4-nitrobenzimidazole **(4013)**

To 2-(2,6-difluorophenyl)-4-nitrobenzimidazole (**4012**) (2.50 g, 9.08 mmol) and 3,3-dimethylallyl bromide (2.00 mL, 17.35 mmol, 190 M%) dissolved in THF (25 mL) was added NaH (60% dispersion in mineral oil) (0.70 g, 17.5 mmol, 190 M%). After stirring overnight at room temperature, the reaction was quenched with MeOH and concentrated. The residue was redissolved in dichloromethane, washed with water and NaCl (sat. aq.), dried

(Na_2SO_4), filtered and concentrated. The product was purified by flash chromatography eluting with ethylacetate/hexane (1:1) and recrystallized from hexane (2.88 g, 8.39 mmol, 92% yield of white powder). mp 130-132 °C; ^{1}H-NMR (200 MHz, CD_2Cl_2): 8.15 (dd, J= 1.0, 8.1 Hz, 1H, H_5), 7.77 (dd, J= 1.0, 8.2 Hz, 1H, H_7), 7.59 (m, 1H, $H_{4''}$), 7.44 (dd, J= 8.1, 8.2 Hz, 1H, H_6), 7.14 (m, 2H, $H_{3'',5''}$), 5.19 (t, J= 6.8 Hz, 1H, $H_{2'}$), 4.73(d, J= 7.0 Hz, 2H, $H_{1'}$), 1.68 (s, 3H, CH_3), 1.62 (s, 3H, CH_3). Anal. ($C_{18}H_{15}F_2N_3O_2$) C,H,N.

EXAMPLE 57

Preparation of 1-(3,3-Dimethylallyl)-2-(2,6-difluorophenyl)-4-aminobenzimidazole (4014)

To 1-(3,3-dimethylallyl)-2-(2,6-difluorophenyl)-4-nitrobenzimidazole (**4013**) (2.00 g, 5.83 mmol) dissolved in glacial acetic acid (20 mL) was added iron powder (8.89 g). After 30 min at reflux, the reaction was concentrated to dryness, diluted with ethyl acetate and washed with $NaHCO_3$. The aqueous layer was back extracted with ethyl acetate and the combined organic solution was washed with $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.), dried (Na_2SO_4), filtered and concentrated. The product was purified by flash chromatography eluting with 4% MeOH/CH_2Cl_2 and recrystallized from hexane (1.73 g, 5.52 mmol, 95% yield of white powder): mp 107-108 °C. ^{1}H-NMR (200 MHz, CD_2Cl_2): 7.54 (m, 1H, $H_{4''}$), 7.16-7.05 (m, 3H, $H_{6,3'',5''}$), 6.80 (dd, J= 1.0, 8.2 Hz, 1H, H_7), 6.55 (dd, J= 1.0, 7.6 Hz, 1H, H_5), 5.20 (t, J= 6.8 Hz, 1H, $H_{2'}$), 4.60 (d, J= 6.8 Hz, 2H, $H_{1'}$), 4.40 (br, 2H, NH_2), 1.66 (s, 3H, CH_3), 1.58 (s, 3H, CH_3). Anal. ($C_{18}H_{17}F_2N_3$) C,H,N.

EXAMPLE 58

Preparation Of *N,N*-Bis-(2,6-Difluorobenzoyl)-4-Chloro-2-Nitroanilide

Examples 58-89 describe the synthesis of 4-substituted benzimidazoles.

In this Example, *N,N*-bis-(2,6-difluorobenzoyl)-4-chloro-2-nitroanilide (400) was prepared. First, 4-chloro-2-nitroaniline (1.05 g, 6.08 mmol) was dissolved in THF:pyridine (1:1) (20 mL), and 2,6-difluorobenzoyl chloride (7) was added (1.9 mL, 15.1 mmol, 250 M%). After 6 hours of mixing, a second aliquot of (7) (0.6 mL, 4.77 mmol, 78 M%). After stirring overnight at room temperature, the reaction was concentrated to dryness. The residue

was redissolved in CH_2Cl_2, washed with $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.), dried (Na_2SO_4), filtered and concentrated. The product was recrystallized from ethylacetate (2.67 g, 5.90 mmol, 97% yield) to produce white crystals. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.15 (d, J= 2.4 Hz. 1H, H_3), 7.67 (dd, J= 2.4, 8.5 Hz, 1H, H_5), 7.51 (d, J= 8.5 Hz, 1H, H_6), 7.36 (m, 2H, $H_{4',4''}$), 6.89 (m, 4H, $H_{3',5',3'',5''}$).

EXAMPLE 59

Preparation Of *N*-(2,6-Difluorobenzoyl)-4-Chloro-2-Nitroanilide

In this Example, *N*-(2,6-difluorobenzoyl)-4-chloro-2-nitroanilide (**500**) was prepared. First, *N,N*-bis-(2,6-difluorobenzoyl)-4-chloro-2-nitroanilide (**400**) (1.00 g, 4.42 mmol) was dissolved in methanol/dioxane (1:1) (40 mL), and sodium hydroxide (0.27 g, 6.75 mmol, 150 M%) was then added to the mixture. After stirring for 30 minutes at room temperature, the reaction was quenched with $NaHSO_4$, diluted with CH_2Cl_2, washed with $NaHCO_3$ (sat aq) and NaCl (sat aq), dried (Na_2SO_4), filtered and concentrated. The product (1.28 g, 4.09 mmol, 93 % yield) was recrystallized from ethylene oxide/hexane (3:1). ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 10.72 (s, 1H, NH), 8.91 (d, J= 9.1 Hz, 1H, H_6), 8.27 (d, J= 2.5 Hz, 1H, H_3), 7.71 (dd, J= 9.1, 2.5 Hz, 1H, H_5), 7.52 (m, 1H, $H_{4'}$), 7.08 (m, 2H, $H_{3',5'}$).

EXAMPLE 60

Preparation Of *N,N*-Bis-(2,6-Difluorobenzoyl)-5-Chloro-2-Nitroanilide

In this Example, *N,N*-bis-(2,6-difluorobenzoyl)-5-chloro-2-nitroanilide (**600**) was prepared. First, 5-chloro-2-nitroaniline (1.02 g, 5.91 mmol) was dissolved in pyridine/THF (1:1) (20 mL), and 2,6-difluorobenzoyl chloride (**7**) (1.50 mL, 11.9 mmol, 200 M%) was then added. After stirring overnight at room temperature, the reaction was concentrated to dryness. The residue was redissolved in CH_2Cl_2, washed with $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.), dried (Na_2SO_4), filtered, and concentrated. The product was recrystallized from ethylacetate (2.50 g, 5.52 mmol, 93% yield of white crystals). ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.12 (dd, J = 8.5, 1.1 Hz, 1H, H_3), 7.58 (AB, J= 2.4, 1.1 Hz, 1H, H_6), 7.57 (AB, J= 2.4, 8.4 Hz, 1H, H_4), 7.36 (m, 2H, $H_{4',4''}$), 6.89 (m, 4H, $H_{3',5',3'',5''}$).

EXAMPLE 61

Preparation Of *N*-(2,6-Difluorobenzoyl)-5-Chloro-2-Nitroanilide

In this Example, *N*-(2,6-difluorobenzoyl)-5-chloro-2-nitroanilide (**700**) was prepared. First, *N,N*-bis-(2,6-difluorobenzoyl)-5-chloro-2-nitroanilide (**600**) (1.00 g, 2.20 mmol) was dissolved in methanol/dioxane (1:1) (20 mL), and then sodium hydroxide (92 mg, 2.30 mmol, 105 M%) was added. After stirring for 30 minutes at room temperature, additional sodium hydroxide (92 mg, 2.30 mmol, 105 M%) was added. After an additional 15 minutes the reaction was quenched with $NaHSO_4$, diluted with CH_2Cl_2, washed with $NaHCO_3$ (sat aq.) and NaCl (sat aq.), dried (Na_2SO_4), filtered and concentrated. The product was recrystallized from ethylene oxide/hexane (3:1) to produce 0.55 g, (1.85 mmol, 84% yield) of white crystals. ^{1}H-NMR (200 MHz, CD_2Cl_2): δ 10.91 (s, 1H, NH), 9.04 (d, J= 2.3 Hz, 1H, H_6), 8.23 (d, J= 9.0 Hz, 1H. H_4), 7.52 (cm, 1H, $H_{4'}$), 7.26 (dd, J= 2.3, 9.0 Hz, 1H, H_4), 7.08 (m, 1H, $H_{3',5'}$).

EXAMPLE 62

Preparation Of *N*-(2,6-Difluorobenzoyl)-2-Amino-3-Nitroanilide

In this Example, *N*-(2,6-difluorobenzoyl)-2-amino-3-nitroanilide (**800**) was prepared according to Method A, described above, with the changes to the starting materials, notable variations, and/or additions to the method indicated as needed. Method A was also used to produce the compounds described in subsequent Examples, as indicated.

First, 3-nitro-1,2-phenylenediamine (13.3 g, 86.85 mmol) and 2,6-difluorobenzoyl chloride (7) (15.33 g, 10.95 mL, 86.85 mmol) were mixed, stirred overnight, and then recrystallized from ethylacetate/hexane to produce 12 g (41 mmol, 48% yield) of yellow crystals. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.23 (s, 1H, NH), 7.99 (dd, J= 8.7, 1.4 Hz, 1H, H_4), 7.71 (dd, J= 7.6 Hz, 1.4 Hz, 1H, H_6), 7.62 (m, 1H, $H_{4'}$), 7.28 (m, 2H, $H_{3',5'}$), 6.91 (s, 2H, NH_2), 6.76 (dd, J= 8.7, 7.6 Hz, 1H, H_5).

EXAMPLE 63

Preparation Of *N*-(2,6-Difluorobenzoyl)-2,3-Dimethyl-6-Nitroanilide

In this Example, *N*-(2,6-difluorobenzoyl)-2,3-dimethyl-6-nitroanilide (**900**) was prepared according to Method A, using 2,3-dimethyl-6-nitroaniline (2.00 g, 12.04 mmol) and

2,6-difluorobenzoyl chloride (7) (1.50 mL, 13.93 mmol, 115 M%). After 3 hours of mixing, an additional (7) (0.50 mL, 4.64 mmol, 40 M%) was added to the mixture. After an additional 5 hours of mixing, the compound was recrystallized from ethylacetate/hexane (1:4) to produce 2.71 g (8.85 mmol, 74% yield) of yellow crystals. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.67 (s, 1H, NH), 7.81(d, J= 8.4 Hz, 1H, H_6), 7.48 (m, 1H, $H_{4'}$), 7.28 (d, J= 8.4 Hz, 1H, H_5), 7.05 (m, 2H, $H_{3',5'}$), 2.44 (s, 3H, CH_3), 2.31 (s, 3H, CH_3).

EXAMPLE 64

Preparation Of *N*-(2,6-Difluorobenzoyl)-3-Methyl-6-Nitroanilide

In this Example, *N*-(2,6-difluorobenzoyl)-3-methyl-6-nitroanilide (**1000**) was prepared according to Method A. First, 5-Methyl-2-nitroaniline (4.95 g, 32.5 mmol) was mixed with 2,6-difluorobenzoyl chloride (7) (4.50 mL, 41.8 mmol, 130 M%), as described. After recrystallization from ethylacetate, 8.71 g (29.8 mmol, 92 % yield) of yellow crystals were produced. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 10.85 (s, 1H, NH), 8.75 (s, 1H, H_2), 8.16 (d, J= 8.6, 1H, H_5), 7.50 (m, 1H, $H_{4'}$), 7.48 (d, J= 8.6, 1H, H_4), 7.06 (m, 2H, $H_{3'}$), 2.50 (s, 3H, CH_3).

EXAMPLE 65

Preparation Of *N*-(2,6-Difluorobenzoyl)-4-Methyl-2-Nitroanilide

In this Example, *N*-(2,6-difluorobenzoyl)-4-methyl-2-nitroanilide (**1100**) was prepared according to Method A. First, 4-methyl-2-nitroaniline (4.95 g, 32.5 mmol) was mixed with 2,6-difluorobenzoyl chloride (7) (4.50 mL, 41.8 mmol, 130 M%), as described. After recrystallization from ethylacetate, 6.69 g (22.9 mmol, 70 % yield) of yellow crystals were produced. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 10.64 (s, 1H, NH), 8.75 (d, J= 8.6, 1H, H_6), 8.06 (s, 1H, H_3), 7.52 (m, 1H, $H_{4'}$), 7.48 (d, J= 8.6, 1H, H_5), 7.06 (m, 2H, $H_{3',5'}$), 2.42 (s, 3H, CH_3).

EXAMPLE 66

Preparation Of *N*-(2,6-Difluorobenzoyl)-4-Bromo-2-Nitroanilide

In this Example, *N*-(2,6-difluorobenzoyl)-4-bromo-2-nitroanilide (**1200**) was prepared according to Method A. First, *N*-(2,6-difluorobenzoyl)-2-nitroanilide (1.20 g, 8.69 mmol) was suspended in 10 mL pyridine/THF (1:1). Bromine (0.5 mL) dissolved in acetic acid (0.5 mL) was then added to the mixture. After stirring for 1 hour at room temperature, the reaction was quenched with $NaHCO_3$ (sat. aq.). The solution was extracted with CH_2Cl_2 and the organic extract was washed with NaCl (sat. aq.), dried (Na_2SO_4), filtered and concentrated. The product was recrystallized from ethylacetate to produce 1.55 g, (4.34 mmol, 50 % yield) of yellow crystals. ^{1}H-NMR (200 MHz, CD_2Cl_2): δ 10.72 (br s, 1H, NH), 8.85 (d J= 9.1 Hz, 1H, H_5), 8.42 (d J= 2.4 Hz, 1H, H_3), 7.84 (ddd, J= 0.5, 2.4, 9.1 Hz, 1H, H_6), 7.52 (m, 1H, $H_{4'}$), 7.07 (m, 2H, $H_{3',5'}$).

EXAMPLE 67

Preparation Of *N*-(2,6-Difluorobenzoyl)-*N*-(2,6-Difluorobenzyl)-4-Bromo-2-Nitroanilide

In this Example, *N*-(2,6-difluorobenzoyl)-*N*-(2,6-difluorobenzyl)-4-bromo-2-nitroanilide (**1400**) was prepared according to Method E. Method E was also used to produce the compounds described in subsequent Examples, with the changes to the starting materials, notable variations, and/or additions to the method indicated as needed.

N-(2,6-difluorobenzoyl)-4-bromo-2-nitroanilide (**1200**) (0.26 g, 0.73 mmol) and 2,6-difluoro-α-bromo-toluene (0.27 g, 1.30 mmol, 180 M%) were dissolved in THF (2 mL), to which NaH (0.15 g, 500 M%) was added. After 6 hours, the reaction was quenched with methanol and concentrated. The residue was redissolved in CH_2Cl_2, washed with $NaHCO_3$ (sat. aq.) and NaCl (sat. aq.), dried (Na_2SO_4), filtered and concentrated. The product was purified by flash chromatography eluting with ethylacetate/hexane (1:4), and recrystallized from diethyl ether/hexane (3:1) to produce 0.26 g, (0.54 mmol, 74% yield) of white crystals. ^{1}H-NMR (200 MHz, DMSO-d_6) (rotamers): δ 8.30 (d, J= 2.3 Hz, 1H, H_3, rotamer 1), 8.25 (d, J= 2.3 Hz, 1H, H_3, rotamer 2), 8.02 (dd, J= 2.3, 8.5 Hz, 1H, H_5, rotamer 1), 7.85 (dd, J= 2.3, 8.5 Hz, 1H, H_5, rotamer 2), 7.68 (m, 1H, $H_{4'}$, rotamer 1), 7.54-7.27 (m, 5H, $H_{6,4''}$ rotamers 1 & $H_{6,4',4''}$ rotamer 2), 7.16-6.94 (m, $H_{3',5',3'',5''}$ rotamers 1&2), 5.63 (d, J=14.3 Hz,

1H, CH_2PhF_2, rotamer 2), 4.99 (br, 1H, CH_2PhF_2, rotamer 1), 4.87 (br, 1H, CH_2PhF_2, rotamer 1), 4.86 (d, J=14.3 Hz, 1H, CH_2Ph, rotamer 2).

EXAMPLE 68

Preparation Of *N*-(2,6-Difluorobenzoyl)-*N*-(2,6-Difluorobenzyl)-4-Chloro-2-Nitroanilide

In this Example, *N*-(2,6-difluorobenzoyl)-*N*-(2,6-difluorobenzyl)-4-chloro-2-nitroanilide (**1500**) was prepared according to Method E, using *N*-(2,6-difluorobenzoyl)-4-chloro-2-nitroanilide (**500**) (600 mg, 1.92 mmol) mixed with 2,6-difluoro-α-bromo-toluene (478 mg, 2.3 mmol). After recrystallization from diethyl ether/hexane (3:1), 620 mg (1.41 mmol, 74%) of white crystals was produced. ^{1}H-NMR (300 MHz, CD_2Cl_2) (rotamers): δ 8.02 (d, J= 2.4 Hz, 1H, H_3, rotamer 1), 7.95 (d, J= 2.4 Hz, 1H, H_3, rotamer 2), 7.57 (dd, J= 8.6, 2.4 Hz, 1H, H_5, rotamer 1), 7.50 (m, 1H, $H_{4''}$, rotamer 1), 7.30 (dd, J= 8.4, 2.4 Hz, 1H, H_5, rotamer 2), 7.35-7.03 (m, 5H, $H_{4''}$ rotamer 2 & $H_{6,4'}$ rotamer 1&2), 6.94-6.68 (m, 8H, $H_{3',5',3'',5''}$, rotamer 1 & 2), 5.84 (d, J= 14.4, 1H, CH_2PhF_2, rotamer 2), 4.94 (br s, 2H, CH_2PhF_2, rotamer 1), 4.82 (d, J= 14.4 Hz, 1H, CH_2PhF_2, rotamer 2).

EXAMPLE 69

Preparation Of *N*-(2,6-Difluorobenzoyl)-*N*-(2,6-Difluorobenzyl)-5-Chloro-2-Nitroanilide

In this Example, *N*-(2,6-difluorobenzoyl)-*N*-(2,6-difluorobenzyl)-5-chloro-2-nitroanilide (**1600**) was prepared according to Method E. First, *N*-(2,6-difluorobenzoyl)-5-chloro-2-nitroanilide (**700**) (1.95 g, 6.24 mmol) and 2,6-difluoro-α-bromo-toluene (1.40 g, 6.76 mmol, 110 M%) were mixed for 2 hours. Then, an additional volume of 2,6-difluoro-α-bromo-toluene (1.30 g, 100 M%) was added. After 5 hours of mixing, another additional volume of 2,6-difluoro-α-bromo-toluene was added (0.75 g, 60 M%) was added . After mixing for 8 hours, purification by flash chromatography, elution with ethyl acetate/hexane (1:4) to produce 2.06 g (4.69 mmol, 75% yield) of white crystals. ^{1}H-NMR (200 MHz, DMSO-d_6) (rotamers): δ 8.08 (d, J= 9.4 Hz, 1H, H_6, rotamer 1), 8.03 (d, J= 8.8 Hz, 1H, H_6, rotamer 2), 7.79-6.91 (m, 16H, $H_{3,4,3',4',5',3'',4'',5''}$ rotamer 1&2), 5.55 (d, J= 14.7, 1H, CH_2PhF_2, rotamer 2),

5.12 (br. 1H, CH_2PhF_2, rotamer 1), 4.99 (d, J= 14.7 Hz, 1H, CH_2PhF_2, rotamer 2), 4.87 (br, 1H, CH_2PhF_2, rotamer 1).

EXAMPLE 70

Preparation Of *N*-(2,6-Difluorobenzoyl)-*N*-(2,6-Difluorobenzyl)-4-Methyl-2-Nitroanilide

In this Example, *N*-(2,6-difluorobenzoyl)-*N*-(2,6-difluorobenzyl)-4-methyl-2-nitroanilide (**1700**) was prepared according to Method E. *N*-(2,6-difluorobenzoyl)-4-methyl-2-nitroanilide (**1100**) (2.00 g, 6.84 mmol) and 2,6-difluoro-α-bromo-toluene (2.12 g, 10.2 mmol, 150 M%) were mixed for 3 hours, and recrystallized from diethyl ether/hexane (3:1) to produce 2.80 g (6.69 mmol, 98% yield) of white crystals. ^{1}H-NMR (300 MHz, DMSO-d_6) (rotamers): δ 7.89 (dd, J= 2.0, 0.9 Hz, 1H, H_3 rotamer 1), 7.87 (dd, J= 2.0, 0.8 Hz, 1H, H_3 rotamer 2), 7.66 (m, 1H, $H_{4'}$ rotamer 1), 7.56 (ddd, J= 8.2, 2.0, 0.9 Hz, 1H, H_5 rotamer 1), 7.43 (m, 1H, $H_{4'}$ rotamer 2), 7.37-7.27 (m, 5H, H_5 rotamer 2, $H_{3',5'}$ rotamer 1, $H_{4''}$ rotamer 1&2) 7.21 (d, J=8.2 Hz, 1H, H_6 rotamer 1), 7.07 (m, 2H, $H_{3',5'}$ rotamer 2), 7.01-6.90 (m, 4H, $H_{3'',5''}$ rotamer 1&2), 6.83 (br d, J= 7.7 Hz, 1H, H_6 rotamer 2), 5.71 (d, J= 14.4 Hz, 1H, $CHPhF_2$ rotamer 2), 4.97 (d, J= 14.4 Hz, 1H, $CHPhF_2$ rotamer 1), 4.83 (d, J= 14.4 Hz, 1H, $CHPhF_2$ rotamer 1), 4.78 (d, J= 14.4 Hz, 1H, $CHPhF_2$ rotamer 2), 2.41 (s, 3H, CH_3 rotamer 1), 2.27 (s, 3H, CH_3 rotamer 2).

EXAMPLE 71

Preparation Of *N*-(2,6-Difluorobenzoyl)-*N*-(2,6-Difluorobenzyl)-5-Methyl-2-Nitroanilide

In this Example, *N*-(2,6-difluorobenzoyl)-*N*-(2,6-difluorobenzyl)-5-methyl-2-nitroanilide (**1800**) was prepared according to Method E. *N*-(2,6-difluorobenzoyl)-3-methyl-6-nitroanilide (**1000**) (2.00 g, 6.84 mmol) and 2,6-difluoro-α-bromo-toluene (2.12 g, 10.2 mmol, 150 M%) were mixed for 3 hours. After recrystallization from diethyl ether/hexane (3:1), 1.92 g (4.59 mmol, 67% yield) of white crystals were produced. ^{1}H-NMR (200 MHz, CD_3OD) (rotamers): δ 7.92 (d, J= 8.5 Hz, 1H, H_6, rotamer 1), 7.89 (d, J= 8.5, 1H, H_6, rotamer 2), 7.60 (m, 1H, $H_{4'}$, rotamer 1), 7.44-6.72 (m, 15H, $H_{3,4,3',5',3'',4'',5''}$ rotamers 1 & $H_{3,4,3',4',5',3'',4'',5''}$ rotamer 2), 5.86 (d, J= 14.3 Hz, 1H, CH_2PhF_2, rotamer 2), 4.98 (br, 2H,

CH_2PhF_2, rotamer 1), 4.88 (d, J= 14.3 Hz, 1H, CH_2PhF_2, rotamer 2), 2.35 (s, 3H, CH_3, rotamer 1), 2.35 (s, 3H, CH_3, rotamer 2).

EXAMPLE 72

Preparation Of *N*-(2,6-Difluorobenzoyl)-*N*-(2,6-Difluorobenzyl)-2-Methyl-6-Nitroanilide

In this Example, *N*-(2,6-difluorobenzoyl)-*N*-(2,6-difluorobenzyl)-2-methyl-6-nitroanilide (**1900**) was prepared according to Method E. First, 2,6-difluorobenzoyl-2-methyl-6-nitroanilide (**11**) (450 mg, 1.54 mmol) and 2,6-difluoro-α-bromo-toluene (351 mg, 1.69 mmol) were mixed. After recrystallization from diethylether/methanol 490 mg (1.17 mmol, 76% yield) of colorless crystals was produced. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.82 (dd, J= 8.0, 1.5 Hz, 1H, H_5), 7.52 (m, 1H, H_{4bz}), 7.51 (dd, 1H, J= 7.9, 1.6 Hz, 1H, H_3), 7.42 (t, 1H, J= 7.9 Hz, H_4), 7.25 (m, 1H, H_{4bn}), 7.12 (m, 2H, $H_{3bz,5bz}$), 6.74 (m, 2H, $H_{3bn,5bn}$), 4.80 (s, 2H, CH_2), 2.17 (s, 3H, CH_3).

EXAMPLE 73

Preparation Of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-5-Bromobenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-5-bromobenzimidazole (**2100**) was prepared according to Method F. Method F was also used to produce the compounds described in subsequent Examples, with the changes to the starting materials, notable variations, and/or additions to the method indicated as needed.

First, 2,6-difluoro-α-bromo-toluene (0.26 g, 0.54 mmol) was dissolved in glacial acetic acid (5 mL). Then, iron powder (**17**) (0.55 g) was added to the mixture. After 30 min, the reaction was concentrated to dryness, diluted with ethyl acetate, and adjusted to pH 7 with $NaHCO_3$ (sat. aq.). The organic solution was collected and washed with $NaHCO_3$ and NaCl, dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography eluting with 2% $MeOH/CH_2Cl_2$ and then recrystallized from 3:1 diethyl ether/hexane to produce 0.14 g (0.33 mmol, 62% yield) of white crystals. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.11 (dd, J= 0.6, 1.9 Hz, 1H, H_4), 7.56 (cm, 1H, $H_{4''}$), 7.41 (AB, J= 1.9, 8.7 Hz, 1H, H_5), 7.40 (AB, J= 0.6, 8.7 Hz, 1H, H_6), 7.26 (cm, 1H, $H_{4'}$), 7.10 (cm, 2H, $H_{3'',5''}$), 6.83 (cm, 2H, $H_{3',5'}$), 5.35 (s, 2H, CH_2PhF_2). Anal. ($C_{20}H_{11}BrF_4N_2$ x3/4H_2O) C,H,N.

EXAMPLE 74

Preparation Of 1-(2,6-Difluorobenzyl)-
2-(2,6-Difluorophenyl)-5-Chlorobenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-5-chlorobenzimidazole (**2200**) was prepared according to Method F. *N*-(2,6-difluorobenzoyl)-*N*-(2,6-difluorobenzyl)-4-chloro-2-nitroanilide (**1500**) (620 mg, 1.41 mmol) and iron powder (**17**) (200 mg) were mixed for 3 hours. After recrystallization, 250 mg (0.64 mmol, 45%) of colorless crystals were produced, with a mp of 136°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.77 (d, J= 1.95 Hz, H_4), 7.55 (m, 1H, $H_{4'}$), 7.42 (d, J= 8.7 Hz, 1H, H_7), 7.27 (dd, J= 8.7, 1.95 Hz, 1H, H_6), 7.26 (m, 1H, $H_{4''}$), 7.09 (m, 2H, $H_{3',5'}$), 6.82 (m, 2H, $H_{3'',5''}$), 5.34 (s, 2H, CH_2). Anal. ($C_{20}H_{11}ClF_4N_2$) C,H,N

EXAMPLE 75

Preparation Of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-6-Chlorobenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-6-chlorobenzimidazole (**2300**) was prepared according to Method F. *N*-(2,6-difluorobenzoyl)-*N*-(2,6-difluorobenzyl)-5-chloro-2-nitroanilide (**1600**) (0.57 g, 1.30 mmol) and iron powder (**17**) (0.43 g) were mixed for 1 hour, and purified by flash chromatography eluted with 2% MeOH/CH_2Cl_2, and recrystallized from diethyl ether/ hexane (3:1), to produce 0.43 g (1.10 mmol, 85% yield) of white crystals. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.73 (dd, J= 0.9, 8.6 Hz, 1H, H_4), 7.56 (m, 1H, $H_{4''}$), 7.51 (d, J= 1.9 Hz, 1H, H_7), 7.29 (dd, J= 1.9, 8.6 Hz, 1H, H_5), 7.27 (m, 1H, $H_{4'}$), 7.09 (m, 2H, $H_{3'',5''}$), 6.84 (m, 2H, $H_{3',5'}$), 5.33 (s, 2H, CH_2PhF_2). Anal. ($C_{20}H_{11}ClF_4N_2$) C,H,N.

EXAMPLE 76

Preparation Of 1-(2,6-Difluorobenzyl)-
2-(2,6-Difluorophenyl)-5-Methylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-5-methylbenzimidazole (**2400**) was prepared according to Method F. Iron powder (**17**) (1.55 g, 3.71 mmol) and iron powder (**17**) (0.79 g) were mixed, and then recrystallized from diethyl ether/hexane (3:1), to

produce 0.85 g (2.30 mmol, 62% yield) of white crystals. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.60-7.49 (cm, 2H, $H_{4,4''}$), 7.37 (d, J= 8.4 Hz, 1H, H_7), 7.24 (m, 2H, $H_{4'}$), 7.14 (m, 1H, H_6), 7.09 (m, 2H, $H_{3'',5''}$), 6.81 (m, 2H, $H_{3',5'}$), 5.34 (s, 2H, CH_2PhF_2), 2.47 (s, 3H, CH_3). Anal. ($C_{21}H_{14}F_4N_2$) C,H,N.

EXAMPLE 77

Preparation Of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-6-Methylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-6-methylbenzimidazole (**2500**) was prepared according to Method F. *N*-(2,6-difluorobenzoyl)-*N*-(2,6-difluorobenzyl)-5-methyl-2-nitroanilide (**1800**) (1.56 g, 3.73 mmol) and iron powder (**17**) (0.79 g) were mixed. After recrystallization from diethyl ether/hexane 0.89 g (2.41 mmol, 64% yield) of white crystals were produced. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.64 (cm, 1H, H_4), 7.52 (m, 1H, $H_{4''}$), 7.30-7.19 (m, 2H, $H_{7,4'}$), 7.14-7.03 (m, 3H, $H_{5,3'',5''}$), 6.81 (m, 2H, $H_{3',5'}$), 5.33 (s, 2H, CH_2PhF_2), 2.48 (s, 3H, CH_3). Anal. ($C_{21}H_{14}F_4N_2$) C,H,N.

EXAMPLE 78

Preparation Of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-7-Methylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-7-methylbenzimidazole (**2600**) was prepared according to Method F. *N*-(2,6-difluorobenzoyl)-*N*-(2,6-difluorobenzyl)-2-methyl-6-nitroanilide (**1900**) (300 mg, 0.72 mmol) and (**20**) (50 mg) were mixed. After recrystallization from ethyl acetate, 149 mg (0.15 mmol, 56% yield) of colorless crystals were produced, with a mp of 177°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): 7.62 (d, J= 8.2 Hz, 1H, H_4), 7.45 (m, 1H, $H_{4'}$), 7.18 (m, 1H, $H_{4''}$), 7.17 (dd, J= 7.3, 8.2, 1H, H_5), 7.08 (d, J= 7.3, H_6), 6.95 (m, 2H, $H_{3',5'}$), 6.70 (m, 2H, $H_{3'',5''}$), 5.64 (s, 2H, CH_2), 2.74 (s, 3H, CH_3). Anal. ($C_{21}H_{14}F_4N_2$) C,H,N.

EXAMPLE 79

Preparation of 2-(2,6-Difluorophenyl)-4,5-Dimethylbenzimidazole

In this Example, 2-(2,6-difluorophenyl)-4,5-dimethylbenzimidazole (**2700**) was produced according to Method F. *N*-(2,6-difluorobenzoyl)-2,3-dimethyl-6-nitroanilide (**900**) (1.40 g, 4.57 mmol) and (**20**) (1.05 g) were mixed for 1 h, and recrystallized from ethylacetate to produce 1.07 g (4.14 mmol, 91% yield) of white crystals. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.49-7.37 (m, 2H, $H_{4',7}$), 7.16-7.07 (m, 3H, $H_{3',5',6}$), 2.54 (br s, 3H, CH_3), 2.42 (s, 3H, CH_3).

EXAMPLE 80

Preparation Of 2-(2,6-Difluorophenyl)-4-Nitrobenzimidazole

In this Example, 2-(2,6-difluorophenyl)-4-nitrobenzimidazole (**2800**) was prepared according to Method F. *N*-(2,6-difluorobenzoyl)-2-amino-3-nitroanilide (**800**) (12 g, 41 mmol) was dissolved in 130 mL of acetic acid, heated to reflux, and stirred for 12 hours. The reaction mixture was cooled to room temperature, neutralized with NaOH (4N), basified with $NaHCO_3$ (1%), and extracted with ethylacetate (3 x 300 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The remaining crystals were recrystallized from ethylacetate/hexane to produce 7.7 g, (28 mmol, 68%) of crystals. ^{1}H-NMR (300 MHZ, CD_2Cl_2): δ 11.00 (s, 1H, NH), 8.23 (dd, J= 8.2, 0.8 Hz, 1H, H_5), 8.21 (dd, J= 8.0, 0.8 Hz, 1H, H_7), 7.54 (m, 1H, $H_{4'}$), 7.45 (dd, J= 8.0, 8.2 Hz, 1H, H_6), 7.13 (m, 2H, $H_{3',5'}$).

EXAMPLE 81

Preparation Of 2-(2,6-Difluorophenyl)-5-Nitrobenzimidazole

In this Example, 2-(2,6-difluorophenyl)-5-nitrobenzimidazole (**2900**) was prepared according to Method F. 2-(2,6-difluorophenyl)-benzimidazole (**11**) (2.00 g, 8.70 mmol) was dissolved in H_2SO_4 (5.0 mL), and HNO_3 (5.0 mL) was added. After 2 hours at room temperature, the reaction was quenched with ice (50 mL), filtered and washed with water yielding a white solid (1.92 g, 80% yield). ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.60 (d, J= 2.2

Hz, 1H, H_4), 8.25 (dd, J= 2.2, 8.9 Hz, 1H, H_7), 7.78 (d, J= 8.9 Hz, 1H, H_6), 7.65 (m, 1H, $H_{4'}$), 7.24 (m, 2H, $H_{3',5'}$).

EXAMPLE 82

Preparation Of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-4,5-Dimethylbenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4,5-dimethylbenzimidazole (**3000**) was prepared according to Method E. 2-(2,6-difluorophenyl)-4,5-dimethylbenzimidazole (**2700**) (0.25 g, 0.97 mmol) and 2,6-difluoro-α-bromo-toluene (0.44 g, 2.12 mmol, 220 M%) were mixed. After flash chromatography, elution with 4% $MeOH/CH_2Cl_2$, and recrystallization from ethylacetate/hexane (1:1) 0.38 g (0.81 mmol, 83% yield) of white crystals was produced. ^{1}H-NMR (300 MHz, CD_3OD): δ 7.63 (cm, 1H, $H_{4'}$), 7.34 (cm, 1H, H_6), 7.30 (cm, 1H, $H_{4''}$), 7.16 (cm, 1H, H_7), 7.13 (cm, 2H, $H_{3',5'}$), 6.85 (cm, 2H, $H_{3'',5''}$), 5.40 (s, 2H, CH_2PhF_2), 2.54 (s, 3H, CH_3), 2.40 (s, 3H, CH_3). Anal. ($C_{22}H_{16}F_4N_2$) C,H,N.

EXAMPLE 83

Preparation Of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-4-Nitrobenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-nitrobenzimidazole (**3100**) was prepared according to Method E. 2-(2,6-difluorophenyl)-4-nitrobenzimidazole (**2800**) (7.7 g, 28 mmol) and 2,6-difluoro-α-bromo-toluene (6.95 g, 33.6 mmol) were mixed as described. After recrystallization from diethyl ether/hexane (3:1), 9.8 g (24.4 mmol, 87%) of slightly brown crystals were produced, with a mp of 169°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.13 (dd, J= 8.1, 0.92 Hz, 1H, H_5), 7.86 (dd, J= 8.1, 0.9 Hz, 1H, H_7), 7.59 (m, 1H, $H_{4'}$), 7.43 (dd, J= 8.1 Hz, H_6), 7.28 (m, 1H, $H_{4''}$), 7.12 (m, 2H, $H_{3',5'}$), 6.84 (m, 2H, $H_{3'',5''}$), 5.44 (s, 2H, CH_2). Anal. ($C_{20}H_{11}F_4N_3O_2$) C,H,N.

EXAMPLE 84

Preparation Of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-5-Nitrobenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-5-nitrobenzimidazole (**3200**) was prepared according to Method E. 2-(2,6-difluorophenyl)-5-nitrobenzimidazole (**2900**) (0.91 g, 3.31 mmol) and 2,6-difluoro-α-bromo-toluene (1.08 g, 5.22 mmol. 160 M%) were mixed, and a second addition of 2,6-difluoro-α-bromo-toluene (0.47 g, 2.27 mmol, 70 M%) was added to the mixture after 1 hour of mixing. After flash chromatography, eluting with ethyl acetate/hexane (1:4), 1.09 g (2.71 mmol, 82% yield) of white crystals were produced. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.69 (dd, J= 0.5, 2.2 Hz, 1H, H_4), 8.23 (dd, J= 2.2, 9.0 Hz, 1H, H_6), 7.59 (dd, J= 0.5, 9.0 Hz, 1H, H_7), 7.59 (m, 1H, $H_{4'}$), 7.28 (m, 1H, $H_{4''}$), 7.12 (m, 2H, $H_{3',5'}$), 6.84 (m, 2H, $H_{3'',5''}$), 5.44 (s, 2H, CH_2PhF_2). Anal. ($C_{20}H_{11}F_4N_3O_2$) C,H,N.

EXAMPLE 85

Preparation Of 4-Amino-1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)Benzimidazole

In this Example, 4-amino-1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole (**3300**) was produced according to Method E. 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-nitrobenzimidazole (**3100**) (9.2 g, 23 mmol) was dissolved in acetic acid (130 mL), and $SnCl_2x2H_2O$ (41.5 g) dissolved in concentrated HCl (35 mL) was added. After stirring for 3 hours at room temperature, the mixture was neutralized with NaOH (4N), basified with $NaHCO_3$ (5%), diluted with water to give a final volume of 3 L, and then extracted with ethylacetate (5 x 300 mL). The combined ethylacetate layers were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by gravity chromatography, eluting with acetone/hexane (1:1) and recrystallized from acetone/hexane/diethylether to produce 3.7 g of pink crystals (10 mmol, 44% yield), with a mp of 178°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.52 (m, 1H, $H_{4'}$), 7.23 (m, 1H, $H_{4''}$), 7.07 (m, 2H, $H_{3',5'}$), 7.06 (dd, J= 8.1, 7.7 Hz, 1H, H_6), 6.82 (d, J= 8.1 Hz, H_7), 6.81 (m, 2H, $H_{3'',5''}$), 6.52 (d, J= 7.7, 0.9 Hz, 1H, H_5), 5.29 (s, 2H, CH_2), 4.42 (s, 2H, NH_2). Anal. ($C_{20}H_{13}F_4N_3$) C,H,N.

EXAMPLE 86

Preparation Of 4-Bromo-1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)Benzimidazole

In this Example, 4-bromo-1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole (**3400**) was produced according to Method E. 4-amino-1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole (**3300**) (800 mg, 2.15 mmol) was suspended in HBr (48%, 7 mL) at 0°C, then $NaNO_2$ (193 mg, 2.8 mmol) in water (1.5 mL) was slowly added. After stirring for 30 min at 0-5°C, the mixture was added to CuBr (373 mg, 2.6 mmol) dissolved in HBr (48%, 3 mL). After 30 min at room temperature, water (250 mL) was added, and the pH adjusted to 5 with KOH 4N. The mixture was extracted with ethylacetate, dried (Na_2SO_4), filtered, and evaporated. The crude brown crystals were purified by gravity chromatography eluting with hexane/acetone (2:1) and recrystallized with diethylether/hexane (3:1) to produce 610 mg, (1.4 mmol, 65% yield) of colorless crystals, with a mp of 147°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.56 (m, 1H, $H_{4'}$), 7.49 (dd, J= 7.7, 0.87 Hz, 1H, H_5), 7.47 (d, J= 7.9 Hz, H_7), 7.26 (m, 1H, $H_{4''}$), 7.18 (dd, J= 8.2, 7.7 Hz, 1H, H_6), 7.09 (m, 2H, $H_{3',5'}$), 6.82 (m, 2H, $H_{3'',5''}$), 5.35 (s, 2H, CH_2). Anal. ($C_{20}H_{11}BrF_4N_2 \times 1/4H_2O$) C,H,N.

EXAMPLE 87

Preparation Of 4-Chloro-1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)Benzimidazole

In this Example, 4-chloro-1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole (**3500**) was prepared according to Method E. 4-amino-1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole (**3300**) (800 mg, 2.15 mmol) was dissolved in concentrated HCl (7 mL) and water (5 mL) at 0°C, then $NaNO_2$ (193 mg, 2.8 mmol) in water (1.5 mL) was slowly added. After 30 min at 0-5°C, the mixture was added to CuCl (256 mg, 2.6 mmol) in concentrated HCl (2 mL) at 0°C. After rising to room temperature over 40 min, the pH was adjusted to pH 5, diluted with water (80 mL), extracted with ethylacetate, dried (Na_2SO_4), filtered, and evaporated. The residue was purified by gravity chromatography eluting with hexane/acetone (2:1) and recrystallized from acetone/hexane to produce 350 mg of yellow crystals (0.90 mmol, 42% yield), with a mp of 163°C. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.56 (m, 1H, $H_{4'}$), 7.43 (dd, J= 8.0, 1.1 Hz, 1H, H_7), 7.31 (dd, J=7.8, 1.1 Hz, 1H,

H_5), 7.26 (m, 1H, $H_{4''}$), 7.24 (dd, J= 8.0, 7.8 Hz 1H, H_6), 7.09 (m, 2H, $H_{3',5'}$), 6.83 (m, 2H, $H_{3'',5''}$). 5.36 (s, 2H, CH_2). Anal. ($C_{20}H_{11}ClF_4N_2$) C,H,N.

EXAMPLE 88

Preparation Of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-4-Acetamidobenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-acetamidobenzimidazole (**3600**) was prepared according to Method E. 4-amino-1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole (**3300**) (0.30 g, 0.81 mmol) was dissolved in THF (3 mL), and acetic anhydride (100 mL, 1.06 mmol) was then added. After 3 hours. additional acetic anhydride (20 mL, 0.21 mmol) was added. After 5 hours, the reaction was concentrated to dryness, diluted with ethyl acetate (50 mL), washed with $NaHCO_3$ (25 mL) and NaCl (25 mL), dried (Na_2SO_4), filtered, and concentrated. The product was recrystallized from diethyl ether/hexane (3:1) to produce 0.32 g (0.77 mmol, 95% yield) of white crystals. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 8.49 (1H, br, NH), 8.20 (d, J= 7.8 Hz, 1H, H_5), 7.56 (m, 1H, $H_{4'}$), 7.26 (t, J= 7.9 Hz, 1H, H_6), 7.26 (m, 1H, $H_{4''}$), 7.19 (d, J= 7.9 Hz, 1H, H_7), 7.10 (m, 2H, $H_{3',5'}$), 6.82 (m, 2H, $H_{3'',5''}$), 5.34 (s, 2H, CH_2PhF_2), 2.21 (s, 3H, Ac). Anal. ($C_{22}H_{15}F_4N_3O$) C,H,N.

EXAMPLE 89

Preparation Of 1-(2,6-Difluorobenzyl)-2-(2,6-Difluorophenyl)-4-*N*,*N*-Dimethylaminobenzimidazole

In this Example, 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)-4-*N*,*N*-dimethylaminobenzimidazole (**3700**) was prepared according to Method E. A slurry of 4-amino-1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole (**3300**) (0.37 g, 1.0 mmol) and sodium borohydride (0.27 g) was added to a mixture of 3 M H_2SO_4 (0.80 mL) and 37% H_2CO (0.50 mL). After the addition was complete, the mixture was concentrated to dryness, diluted with ethyl acetate, washed with Na_2CO_3 and NaCl, dried (Na_2SO_4), filtered, concentrated and recrystallized from diethyl ether/hexane (3:1) to produce 0.34 g (0.85 mmol. 85% yield) of white crystals. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.51 (m, 1H, $H_{4'}$), 7.23 (m, 1H, $H_{4''}$). 7.13 (t, J= 8.0 Hz, 1H, H_6), 7.06 (m, 2H, $H_{3',5'}$), 6.90 (d, J= 8.0 Hz. 1H, H_5), 6.80

(m, 2H. $H_{3'',5''}$), 6.48 (d, J= 8.0 Hz, 1H, H_7), 5.30 (s, 2H, CH_2PhF_2), 3.18 (s, 6H. $N(CH_3)_2$). Anal. ($C_{22}H_{17}F_4N_3$) C,H,N.

EXAMPLE 90

Reverse Transcriptase Assay

In this Example, the effects of various compounds were tested for their ability to inhibit the RNA-dependent DNA polymerase (*i.e.*, RT) activity of purified RT. Briefly, in the basic assay (*e.g.*, controls), purified RT protein (0.015 mg/mL) was incubated in a 100 μL reaction mixture containing 25 mM Tris (pH 8.0), 75 mM KCl, 8 mM $MgCl_2$, 2 mM dithiothreitol, 0.1 units poly (rC)-oligo(dG), 0.01 mM dGTP, 1x BSA, 10 mM CHAPS, 0.025 mCi (α ^{35}S)dGTP (specific activity, 1000 Ci/mmol), for 1 hour at 37°C. In the test assays, various concentrations of anti-RT compounds were included in the reaction mixture. The assays were stopped by adding 1 mL of 10% trichloroacetic acid and 30 μL of denatured and sheared salmon sperm DNA (10 mg/mL) as a carrier. The labeled polymer was collected on Whatman glass GF/C filters by suction filtration, washed with 10% trichloroacetic acid and 95% ethanol, and the radioactivity was counted.

Figure 7 shows the structures, formulae, weight, and the percentage of various compounds produced using the methods of the present invention, as well as remaining HIV RT activity as reported as a percent of the control in HIV RT inhibition assays.

EXAMPLE 91

Cytopathic Cell Killing Anti-Viral Assay

In this Example, the antiviral and cellular toxicity of NNRTIs was investigated, using the cytopathic cell killing assay described by Yang (Yang *et al.*, "Characteristics of a Group of Non-nucleoside Reverse Transcriptase Inhibitors with Structural Diversity and Potent Anti-Human Immunodeficiency Virus Activity," Leukemia 9:S75-S85 [1995]). Briefly, in this method cells (*e.g.*, the CEM-SS cell line, available from the NIAID AIDS Research and Reference Program [ARRRP]) were seeded at a density of 5 x 10^3 cells/well, into the wells of a 96-well microtiter plate. The cells were then infected with HIV virus (either mutant or WT), at a multiplicity of infection (MOI) previously determined to provide complete cell killing by 6 days of culture post-infection (*e.g.*, MOI of 0.01-0.05). Each of the HIV isolates

was pre-titered to induce equivalent levels of infection based on cell killing or virus production, prior to their use in these assays. A range of test compound concentrations was added to the wells in triplicate (*e.g.*, serial half-log dilutions) to evaluated inhibition of HIV infection. Controls for each assay included drug controls (drug colorimetric control wells), drug cytotoxicity control wells (cells with drug), virus control wells (cells with virus), and cell viability controls (cells only). Positive control drugs (*e.g.*, AZT and ddC) were run in parallel as positive control drugs.

After six days of incubation at 37°C, cell viability was determined spectrophotometrically at 450 nm for each well, using the metabolic reduction of XTT to a soluble colored formazan. (*See*, Gartner and Popovic, "Virus Isolation and Production, *in* Aldovini and Walker (eds.), *Techniques in HIV Research*, Stockton Press, NY, pp. 69-63 [1991]; and Nara and Fischinger, "Quantitative Infectivity Assay for HIV-1 and HIV-2," Nature 332:469-470 [1988]).

Antiviral and toxicity data were reported as the quantity of drug required to inhibit 50% of virus-induced cell killing or virus production (EC_{50}), and the quantity of drug required to reduce cell viability by 50% (IC_{50}). The *in vitro* therapeutic index (TI_{50}) was defined as the fold-difference between the EC_{50} and IC_{50}. The results for the various compounds are included in Figures 8 and 19. In addition, graphs showing the summary data for three compounds are shown in Figures 20-22. Figure 20 shows the graph for compound **33**. As indicated in this Figure, **33** exhibited very effective therapeutic dose. Figure 21 shows the graph for compound **34**, another compound that also exhibited an effective therapeutic dose. Figure 22 shows the graph for compound **2100**, a compound that was found to be inactive.

EXAMPLE 92

Comparisons Of Inactive Compounds With Active Compounds

RT inhibition activity of previously described 5, 6, or 7-substituted 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole compounds show that substituents with H, CH_3, Cl, Br, and $N(CH_3)_2$ were found to inhibit HIV RT, while substitutions with NO_2, and NHAc did not inhibit the enzyme. These results are illustrated in Figure 11. Although it is not necessary for an understanding of the present invention, it was determined that electron donating or halogen groups apparently increase RT inhibition activity, while electron withdrawing groups decrease inhibition activity. Furthermore, it is apparent that substitution

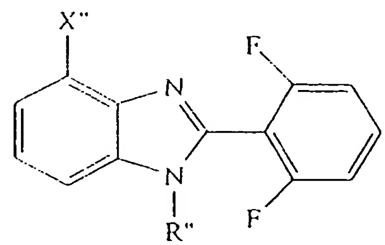
in the 4.6 positions gave increased RT inhibition activity compared to substitutions at the 5 or 7 positions. In addition, it was observed that substitutions of the 4 position with electron donating or halogen groups led to greater HIV RT inhibition than substitution at the 6 position. These results are summarized in Figures 16 and 17.

From the above, it is clear that the present invention provide compositions and methods for the treatment of HIV infection. In particular. the present invention provides non-nucleoside inhibitors of reverse transcriptase (RT). In particular, the present invention relates to stable analogues of 1-(2,6-difluorophenyl)-1H,3H-thiazolo[3,4-a]benzimidazole. effective in the inhibition of human immunodeficiency virus (HIV) RT, with particular activity against HIV-1 RT. Furthermore. the present invention provides highly purified compositions with high activity against HIV-1 RT mutants that are refractory to inhibition with other non-nucleoside HIV-1 RT compounds.

All publications and patents mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

CLAIMS

1. A 1-aryl-2-(2,6-difluorophenyl)benzimidazole composition with general structure:

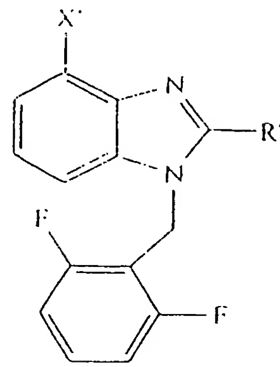


wherein X" is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine; and wherein R" is selected from the group consisting of 2,6-difluorobenzyl, benzyl, ethylbenzyl, 2,6-dichlorobenzyl, 2,3,4,5,6-pentafluorobenzyl, pyridylmethyl, benzenesulfonyl, 2,6-difluorobenzoyl, and 3,3-dimethylallyl.

2. The 1-aryl-2-(2,6-difluorophenyl)benzimidazole of Claim 1, wherein X" is selected from the group consisting of methoxyl and acetamide, and wherein R" is 2,6-difluorobenzyl.

3. The 1-aryl-2-(2,6-difluorophenyl)benzimidazole of Claim 1, wherein R" is 2,6-difluorobenzyl.

4. A 1-(2.6-difluorophenyl)-2-benzimidazole composition with general structure:

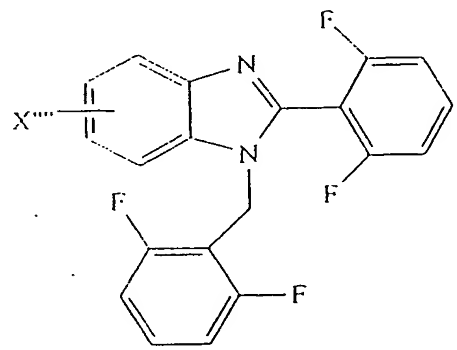


wherein X' is selected from the group consisting of H, methyl, ethyl, cyano. methoxyl, nitro. amine. acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine; and wherein R' is selected from the group consisting of phenyl, formyl. isopropyl. H, methyl, cyclopropyl, hydroxymethyl, 2,6-difluorobenzyloxymethyl, 2,6- difluorophenyl, 2-fluoro-6-methoxylphenyl, methylphenyl, pyridyl, and naphthyl.

5. The 1-(2,6-difluorophenyl)-2-benzimidazole of Claim 4. wherein X' is selected from the group consisting of methoxyl and acetamide, and wherein R' is 2.6-difluorophenyl.

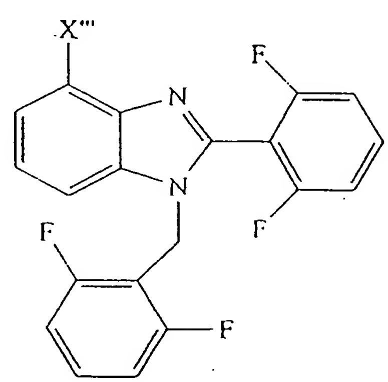
6. The 1-(2,6-difluorophenyl)-2-benzimidazole of Claim 4, wherein R' is 2,6-difluorophenyl.

7. A 4-, 5-, 6-, or 7-substituted-1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole composition of general structure:



wherein X'''' is selected from the group consisting of 4-methyl, 5-methyl, 6-methyl, 7-methyl, 4,5-dimethyl, 4,6-dimethyl, 4-chloro, 5-chloro, 6-chloro, 4-bromo, 5-bromo, 4-nitro, and 5-nitro.

8. A 4-substituted-1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazole composition of the general structure:



wherein X''' is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine.

9. A method for treatment of human immunodeficiency virus infection, comprising the steps of:

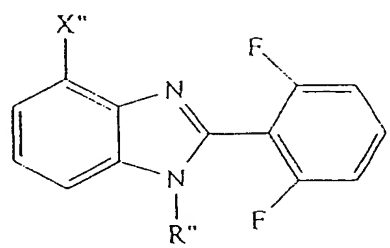
a) providing: i) a subject suspected of being infected with human immunodeficiency virus; and ii) a composition having anti-reverse transcriptase activity, wherein said composition comprises at least one substituted benzimidazole, wherein said substituted benzimidazole contains at least one substitution at the C-2 site, and at least one substitution at the N-1 site;

b) exposing said subject to said composition; and

c) observing for inhibition of said anti-reverse transcriptase activity.

10. The method of Claim 9, wherein said human immunodeficiency virus is HIV-1.

11. The method of Claim 9, wherein said substituted benzimidazole is of the general structure:

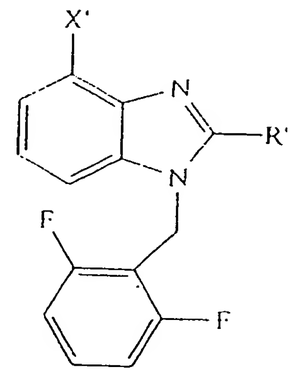


wherein X" is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine; and wherein R" is selected from the group consisting of 2,6-difluorobenzyl, benzyl, ethylbenzyl, 2,6-dichlorobenzyl, 2,3,4,5,6-pentafluorobenzyl, pyridylmethyl, benzenesulfonyl, 2,6-difluorobenzoyl, and 3,3-dimethylallyl.

12. The method of Claim 11, wherein X" is selected from the group consisting of consisting of methoxyl and acetamide, and wherein R" is 2,6-difluorobenzyl.

13. The method of Claim 11, wherein R" is 2,6-difluorobenzyl.

14. The method of Claim 9, wherein said substituted benzimidazole is of the general structure:

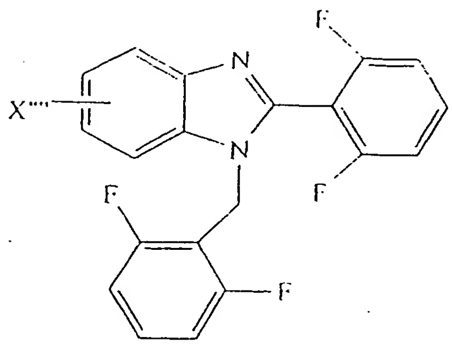


wherein X' is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine; and wherein R' is selected from the group consisting of phenyl, formyl, isopropyl, H, methyl, cyclopropyl, hydroxymethyl, 2,6-difluorobenzyloxymethyl, 2,6-difluorophenyl, 2-fluoro-6-methoxylphenyl, methylphenyl, pyridyl, and naphthyl.

15. The method of Claim 14, wherein X' is selected from the group consisting of methoxyl and acetamide, and wherein R' is 2,6-difluorophenyl.

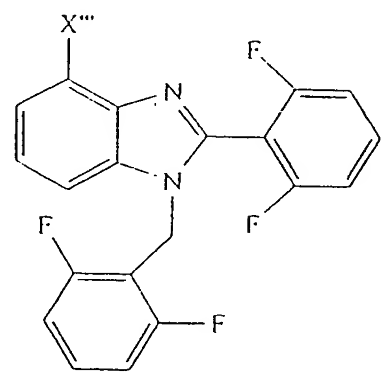
16. The method of Claim 14, wherein R' is 2,6-difluorophenyl.

17. The method of Claim 9, wherein said substituted benzimidazole is of the general structure:



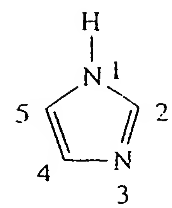
and wherein X'''' is selected from the group consisting of methyl, 4-methyl, 5-methyl, 6-methyl, 7-methyl, 4,5-dimethyl, 4,6-dimethyl, 4-chloro, 5-chloro, 6-chloro, 4-bromo, 5-bromo, 4-nitro, and 5-nitro.

18. The method of Claim 9, wherein substituted benzimidazole is of the general structure:

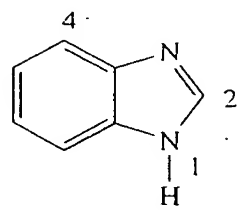


and wherein X''' is selected from the group consisting of H, methyl, ethyl, cyano, methoxyl, nitro, amine, acetamide, methylamine, dimethylamine, propan-2-ol, isopropenyl, bromine and chlorine.

FIGURE 1



IMIDAZOLE



BENZIMIDAZOLE

FIGURE 2

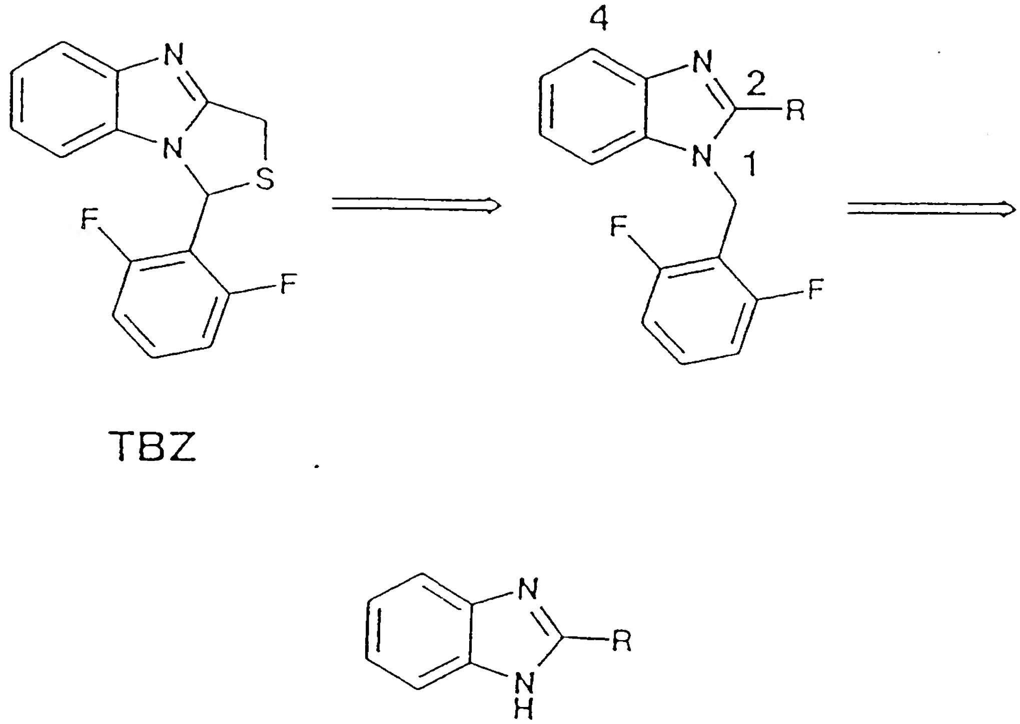
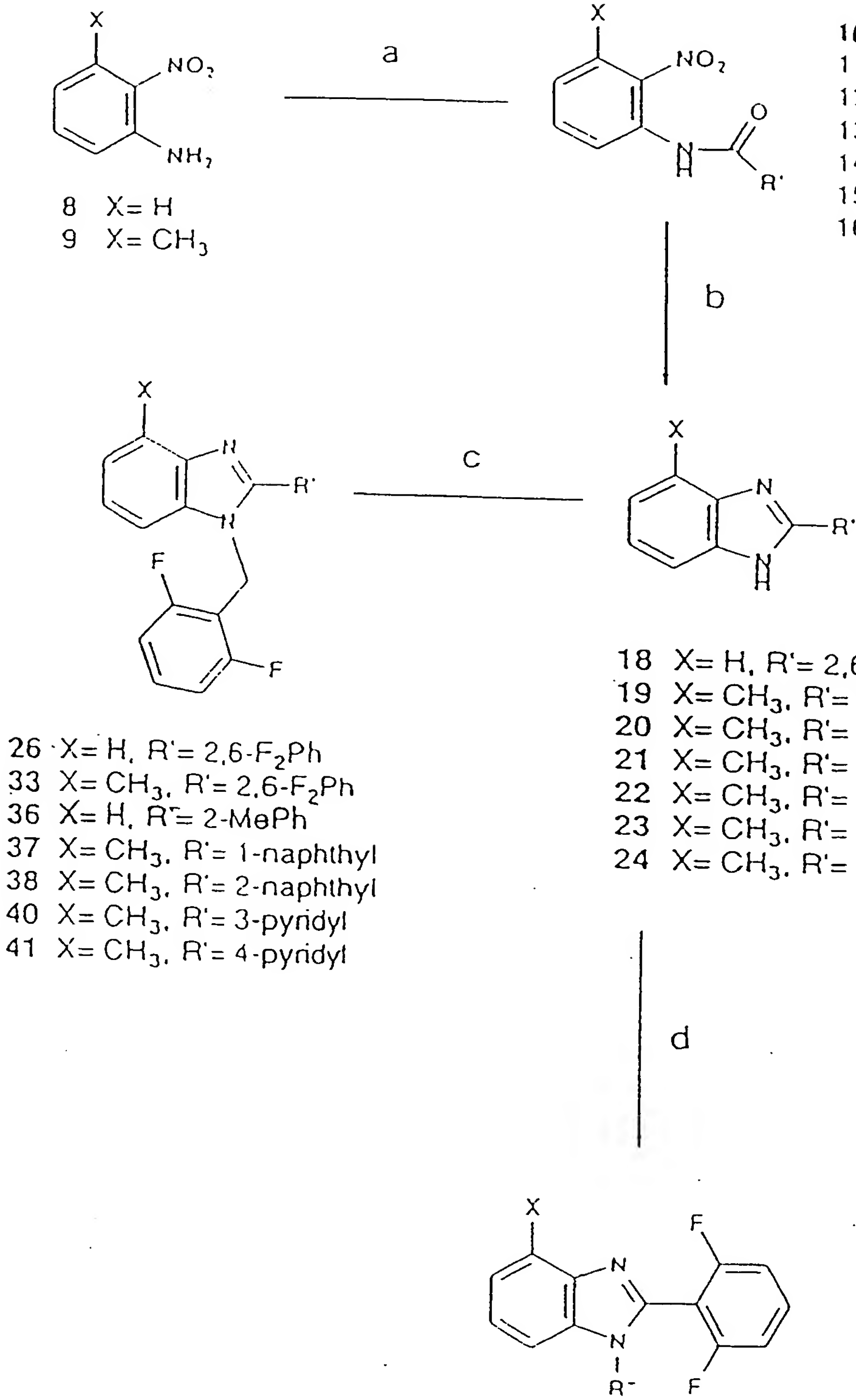


FIGURE 3



8 X= H
9 X= CH_3

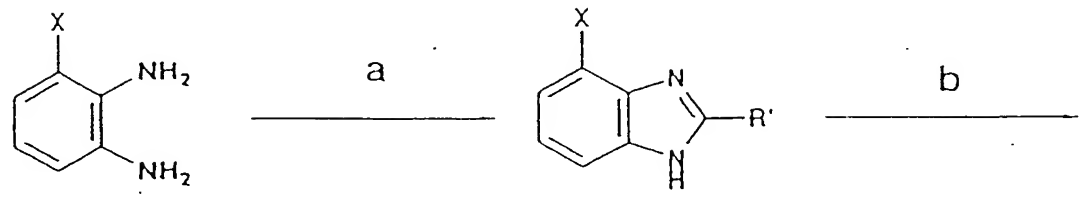
10 X= H. R'= 2,6-F2Ph
11 X= CH_3. R'= 2,6-F2Ph
12 X= CH_3. R'= 4-pyridyl
13 X= CH_3. R'= 2-MePh
14 X= CH_3. R'= 1-naphthyl
15 X= CH_3. R'= 2-naphthyl
16 X= CH_3. R'= 3-pyridyl

18 X= H, R'= 2,6-F_2Ph
19 X= CH_3, R'= 2,6-F_2Ph
20 X= CH_3, R'= 2-MePh
21 X= CH_3, R'= 1-naphthyl
22 X= CH_3, R'= 2-naphthyl
23 X= CH_3, R'= 3-pyridyl
24 X= CH_3, R'= 4-pyridyl

26 X= H, R'= 2,6-F_2Ph
33 X= CH_3, R'= 2,6-F_2Ph
36 X= H, R'= 2-MePh
37 X= CH_3, R'= 1-naphthyl
38 X= CH_3, R'= 2-naphthyl
40 X= CH_3, R'= 3-pyridyl
41 X= CH_3, R'= 4-pyridyl

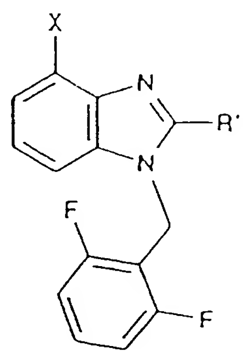
28 X= H. R"= Bn
29 X= CH_3. R"= Bn
30 X= CH_3. R"=$BnCl_2$
42 X= CH_3. R"= 2,3,4,5,6-F_5Bn
43 X= CH_3. R"= 3-pyridyl
45 X= H. R"=$PhSO_2$
46 X= CH_3. R"=$PhSO_2$
47 X= H. R"= 2,6-F_2Bz

FIGURE 4



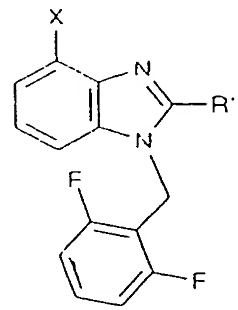
1 $X = H$
3 $X = CH_3$

2 $X = H$, $R' = CH_2OH$
c 4 $X = CH_3$, $R' = CH_2OH$
5 $X = CH_3$, $R' = CH_2OTBDMS$
6 $X = CH_3$, $R' = iPr$



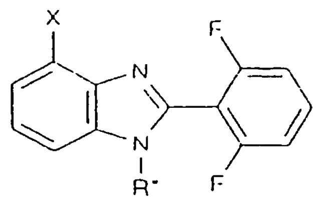
31 $X = H$, $R' = CH_2OTBDMS$
32 $X = H$, $R' = CH_2O(2,6\text{-}F_2Bn)$ d
48 $X = CH_3$, $R' = CH_2OH$
f e 49 $X = CH_3$, $R' = H$
50 $X = CH_3$, $R' = CHO$
34 $X = CH_3$, $R' = iPr$
35 $X = H$, $R' = CH_3$
39 $X = H$, $R' = Ph$

FIGURE 5



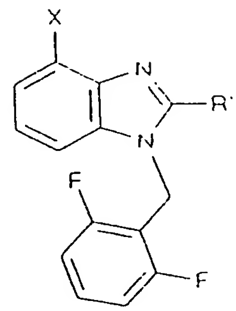
No.	X	R'	formula	mp, °C	anal.	%inhibn (10μM)	IC_{50} (μM)
39	H	Ph	$C_{20}H_{14}F_2N_2$	127-129	C,H,N	77	16
26	H	2,6-F_2Ph	$C_{20}H_{12}F_4N_2$	138-140	C,H,N	93	0.11
33	CH_3	2,6-F_2Ph	$C_{21}H_{14}F_4N_2$	182-186	C,H,N	92	0.20
36	H	2-CH_3-Ph	$C_{21}H_{16}F_2N_2$	138-140	C,H,N	71	
41	CH_3	4-Py	$C_{20}H_{15}F_2N_3$	171-172	C,H,N	70	
40	CH_3	3-Py	$C_{20}H_{15}F_2N_3$	186-188	C,H,N	35	
4007	CH_3	4-CN-Ph	$C_{22}H_{15}F_2N_3$	207-208	C,H,N	26	
37	CH_3	1-Nap	$C_{25}H_{18}F_4N_3$	121-123	C,H,N	2	
38	CH_3	2-Nap	$C_{25}H_{18}F_4N_3$	175-176	C,H,N	8	
TZB			$C_{15}H_{10}F_2N_2S$			84	0.5

FIGURE 6



No.	X	R"	formula	mp, °C	anal.	%inhibn (10μM)	IC_{50} (10μM)
26	H	2,6-F_2Bn	$C_{20}H_{12}F_4N_2$	138-140	C,H,N	93	0.11
33	CH_3	2,6-F_2Bn	$C_{21}H_{14}F_4N_2$	182-186	C,H,N	92	0.20
28	H	Bn	$C_{20}H_{14}F_2N_2$	122-125	C,H,N	71	18.6
29	CH_3	Bn	$C_{21}H_{16}F_2N_2$	112-117	C,H,N[a]	87	1.6
30	CH_3	2,6-Cl_2Bn	$C_{21}H_{14}Cl_2F_2N_2$	202-203	C,H,N	58	
42	CH_3	2,3,4,5,6-F_5Bn	$C_{21}H_{11}F_7N_2$	155-156	C,H,N	36	
43	CH_3	CH_2(3-Py)	$C_{20}H_{15}F_4N_3$	131-132	C,H,N	43	
45	H	$PhSO_2$	$C_{19}H_{12}F_2N_2SO_2$	104-106	C,H,N	52	
46	CH_3	$PhSO_2$	$C_{20}H_{14}F_2N_2SO_2$	134-135	C,H,N	39	
47	H	2,6-F_2Bz	$C_{20}H_{10}F_4N_2O$	144-146	C,H,N	8	

FIGURE 7

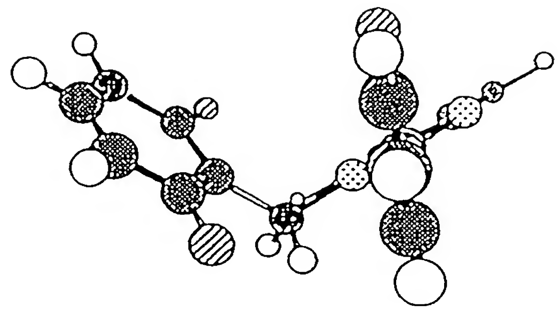


No.	X	R'	formula	mp, °C	anal.	%inhibn (10 μM)
39	H	Ph	$C_{20}H_{14}F_2N_2$	127-129	C,H,N	77
50	CH_3	CHO	$C_{16}H_{12}F_2N_2O$	144-146	C,H,N	59
34	CH_3	iPr	$C_{18}H_{18}F_2N_2$	151-153	C,H,N	53
49	CH_3	H	$C_{15}H_{12}F_2N_2$	98-100	C,H,N	40
35	H	CH_3	$C_{15}H_{12}F_2N_2$	99-100	C,H,N	22
48	CH_3	CH_2OH	$C_{16}H_{14}F_2N_2O$	203-205	C,H,N	12
32	H	CH_2O(2,6 - F_2Bn)	$C_{22}H_{16}F_4N_2O$	107-109	C,H,N	7

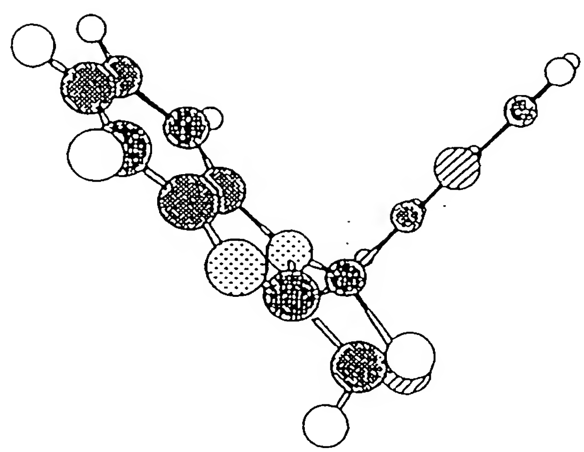
FIGURE 8

Isolate	33	26	TZB	TIBO
NL4-3 (WT)	0.5	1.85	1.7	0.3
L74V	0.1	0.46	0.7	0.2
A98G	1.4	4.75	17.7	11
L1001	0.3	1.36	12.2	17.4
K101E	16.7	>20	>20	17.4
K103N	8.1	12.9	>20	17.4
V106A	20	>20	>20	12.5
V108I	2.8	10.4	9.7	2.4
V179D	0.5	2.3	3.1	6.2
Y181C	6	15.2	16.3	4.2
Y188C	2.3	11.7	>20	>17.4
4xAZT	0.1	0.27	1.5	0.3
4xAZT/L1001	0.2	0.84	1.7	>17.4
4xAZT/Y181C	3.5	>20	14.5	2.0

FIGURE 9

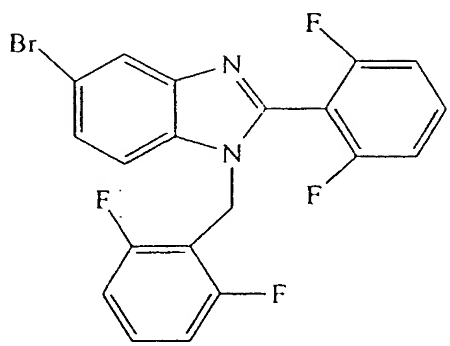


39

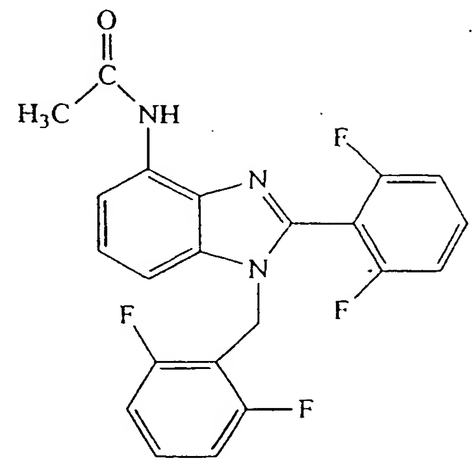


TBZ

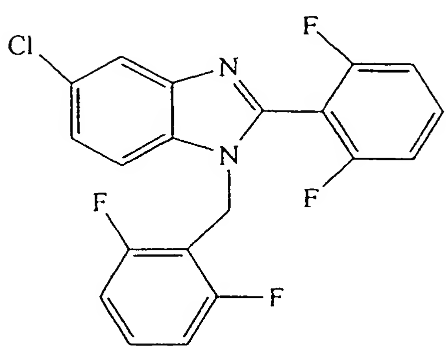
FIGURE 10



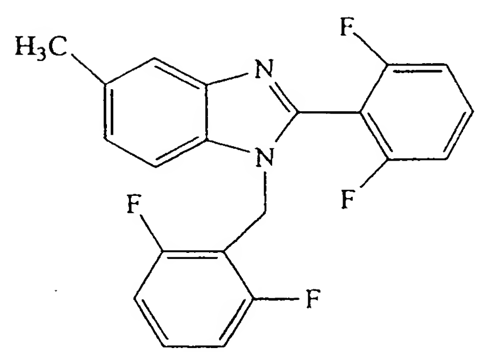
(2100)



(3600)



(2200)



(2400)

FIGURE 11

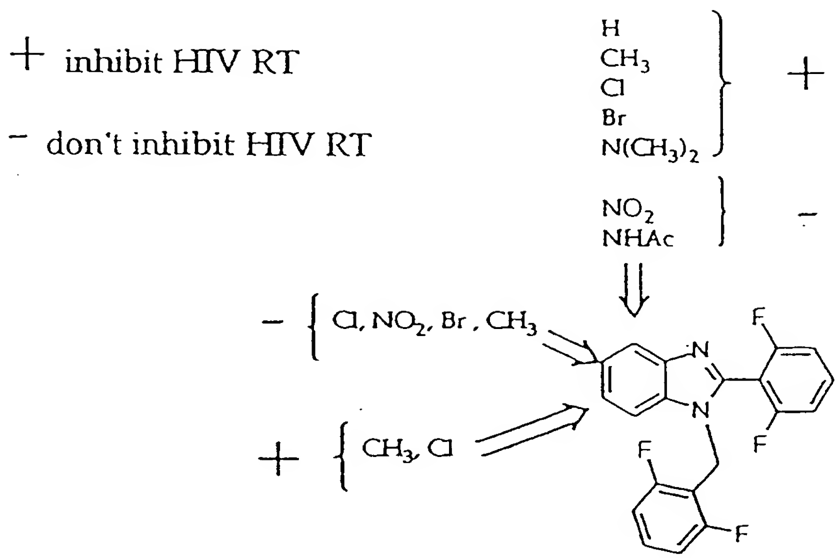

+ inhibit HIV RT
- don't inhibit HIV RT
H
CH3
Cl
Br
N(CH3)2
+
NO2
NHAc
-
- Cl, NO2, Br, CH3
+ CH3, Cl
N
N
F
F
F
F

FIGURE 12

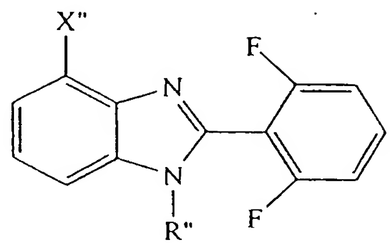


FIGURE 13

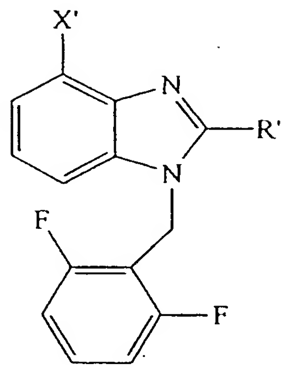
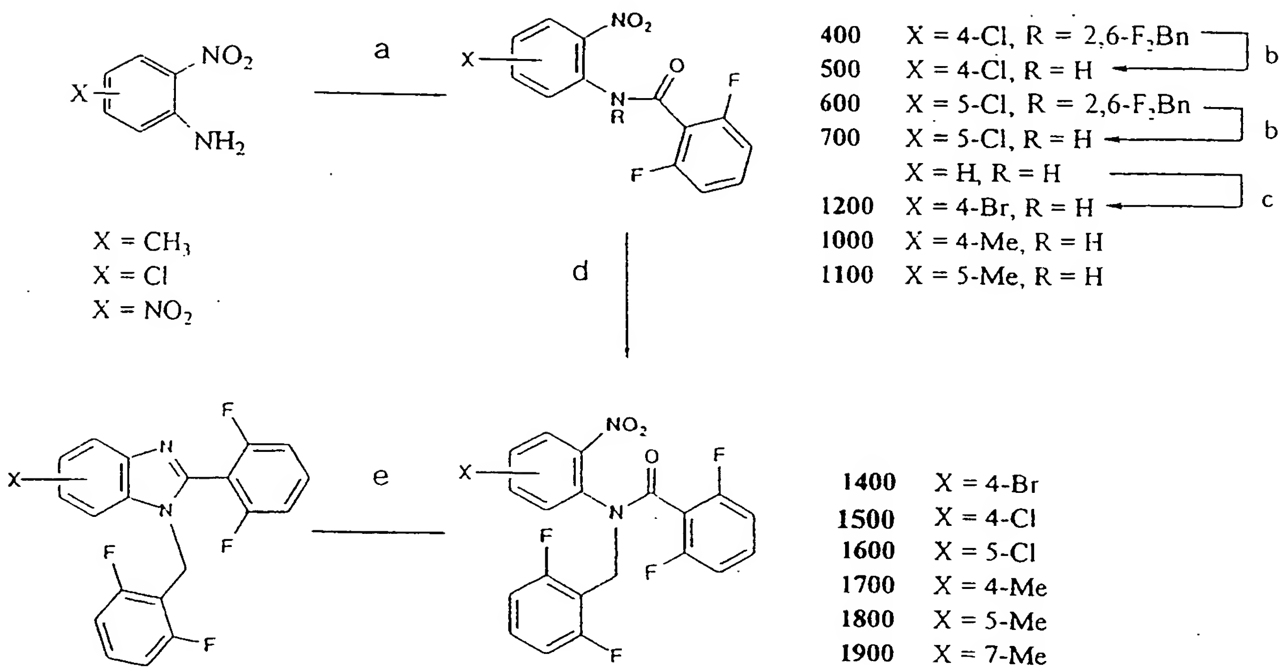


FIGURE 14



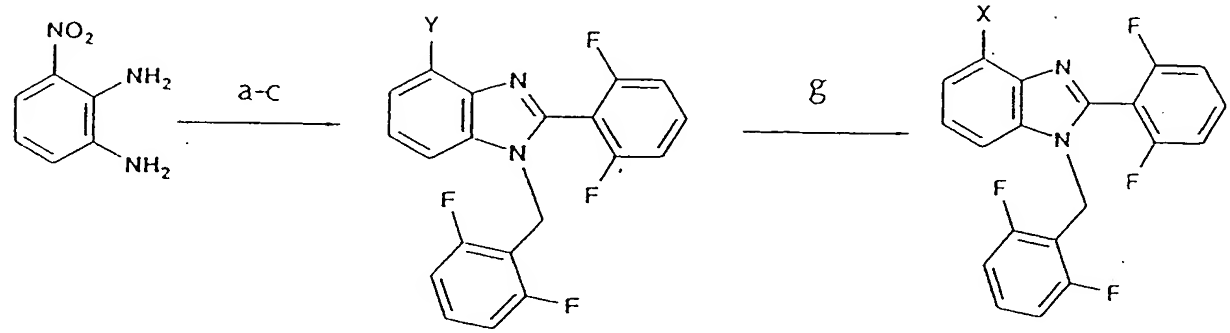
X = CH_3
X = Cl
X = NO_2

400 X = 4-Cl, R = 2,6-F_2Bn
500 X = 4-Cl, R = H
600 X = 5-Cl, R = 2,6-F_2Bn
700 X = 5-Cl, R = H
X = H, R = H
1200 X = 4-Br, R = H
1000 X = 4-Me, R = H
1100 X = 5-Me, R = H

1400 X = 4-Br
1500 X = 4-Cl
1600 X = 5-Cl
1700 X = 4-Me
1800 X = 5-Me
1900 X = 7-Me

2100 X = 5-Br
2200 X = 5-Cl
2300 X = 6-Cl
2400 X = 5-Me
2500 X = 6-Me
2600 X = 7-Me

FIGURE 15



3100 Y = NO_2

d

3300 Y = NH_2

e

3600 Y = NHAc

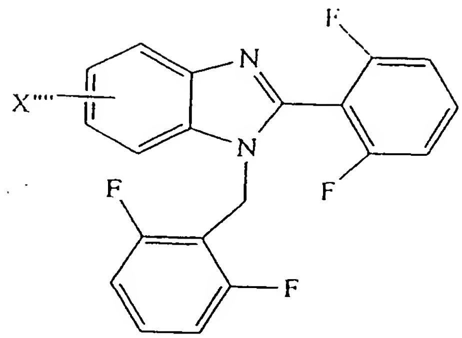
f

3700 Y = $N(CH_3)_2$

3400 X= Br

3500 X = Cl

FIGURE 16

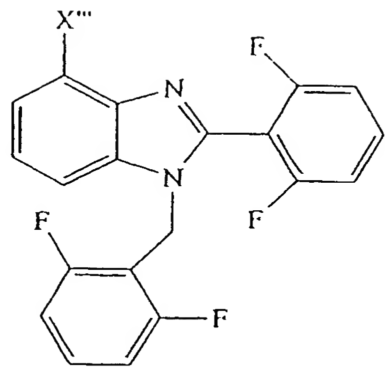


No.	X''''	formula	mp, °C	anal.	% inhibition (1 μM)
26	H	$C_{20}H_{12}F_4N_2$	138-140	C,H,N	58
33	4-CH_3	$C_{21}H_{14}F_4N_2$	182-186	C,H,N	71
2400	5-CH_3	$C_{21}H_{14}F_4N_2$	147-149	C,H,N	27
2500	6-CH_3	$C_{21}H_{14}F_4N_2$	172-173	C,H,N	51
2600	7-CH_3	$C_{21}H_{14}F_4N_2$	177-178	C,H,N	2
2800	4,5-CH_3	$C_{22}H_{16}F_4N_2$	176-177	C,H,N	36

FIGURE 17

No.	X	formula	mp, °C	anal.	% inhibition (1 μM)
3500	4-Cl	$C_{20}H_{11}ClF_4N_2$	163-164	C,H,N	75
2200	5-Cl	$C_{20}H_{11}ClF_4N_2$	136-137	C,H,N	48
2300	6-Cl	$C_{20}H_{11}ClF_4N_2$	152-153	C,H,N	69
3400	4-Br	$C_{20}H_{11}BrF_4N_2$	147-148	C,H,N	78
2100	5-Br	$C_{20}H_{11}BrF_4N_2$	155-156	C,H,N	43
3100	4-NO_2	$C_{20}H_{11}F_4N_3O_2$	168-170	C,H,N	51
2900	5-NO_2	$C_{20}H_{11}F_4N_3O_2$	168-169	C,H,N	30

FIGURE 18



No.	R	formula	mp, °C	anal.	%inhibn (1μM)	IC_{50} (μM)	EC_{50} (μM)
33	CH_3	$C_{21}H_{14}F_4N_2$	182-186	C,H,N	71	0.20	0.44
5006	OCH_3	$C_{21}H_{14}F_4N_2O$	154-155	C,H,N	85	0.0073	0.0046
5011	$NAcCH_3$	$C_{23}H_{17}F_4N_3O$	155-156	C,H,N	77	0.32	0.02
4011	CH_2CH_3	$C_{22}H_{16}F_4N_2$	165-166	C,H,N	50	17.5	0.82
3100	NO_2	$C_{20}H_{11}F_4N_3O$	168-170	C,H,N	51	1.88	2.40
3300	NH_2	$C_{20}H_{13}F_4N_3$	168-170	C,H,N	69	0.28	0.46
3400	Br	$C_{20}H_{11}BrF_4N_2$	147-148	C,H,N	78	1.61	0.37
3500	Cl	$C_{20}H_{11}ClF_4N_2$	163-164	C,H,N	75	2.63	0.44
3600	NHAc	$C_{22}H_{15}F_4N_3O$	194-195	C,H,N	24	54.7	1.48
5012	$NHCH_3$	$C_{21}H_{15}F_4N_3$	194-195	C,H,N	24	4.94	1.70
3700	$N(CH_3)_2$	$C_{22}H_{17}F_4N_3$	155-156	C,H,N	77	40.0	2.37

FIGURE 19

Cross Resistance Profile of 4-Substituted
1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazoles in Cytopathic Cell Killing Assay

Isolate	CH_3	OCH_3	Et	Cl	NH_2	NHAc	$NAcCH_3$	$NHCH_3$	nevir.	TZB
NL4-3	0.5	0.06	1.1	0.4	0.5	1.6	0.04	2.6	0.04	1.0
L74V	0.3	0.08	1.5	0.5	0.3	1.2	0.07	3.9	0.04	0.8
A98G	2.7	0.3	8.0	5.0	1.5	4.3	0.1	8.5	0.8	10
L100I	0.3	0.1	0.6	0.2	1.3	2.1	1.7	0.4	0.2	6.6
K101E	>10	3.3	>20	>20	>20	>20	0.6	>20	1.1	>10
K103N	>20	>20	>20	>20	>20	>20	>10	>20	>10	>20
V106A	>10	1.4	>20	>10	>20	>20	0.05	>20	>10	>10
V108I	2.8	2.5	3.0	3.6	>20	5.3	>10	>20	0.4	5.7
V179D	0.7	0.2	1.8	0.8	0.3	1.7	0.1	3.8	0.2	3.9
Y181C	4.3	0.3	>10	7.3	6.0	>10	0.4	>10	4.9	>10
Y188C	3.0	0.3	5.5	5.4	2.7	>10	0.5	>20	>0.5	>20
4XAZT	0.1	0.6	3.0	0.2	0.2		>10	>10	>0.5	1.1
4XAZT /L100I	0.2		0.6	0.2	0.3		1.8	1.0	0.1	1.1
4XAZT /Y181C	3.5		>20	>20	>10		>10	>20	3.0	>10

FIGURE 20

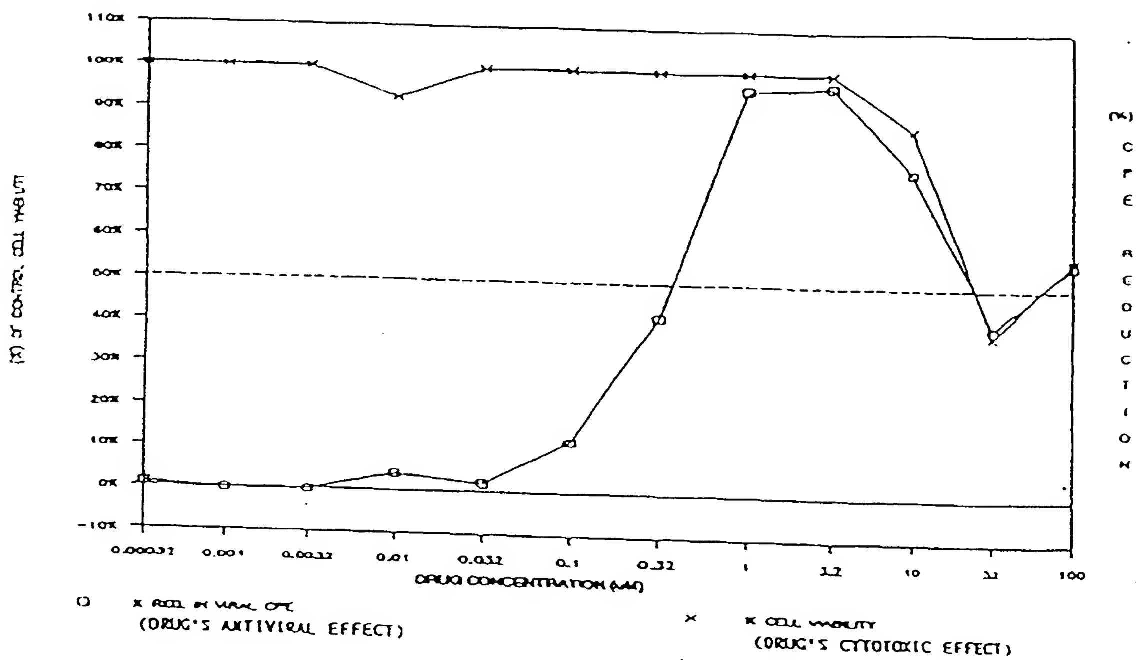

110%
100%
90%
70%
60%
50%
40%
30%
20%
10%
0%
-10%
0.00032
0.001
0.0032
0.01
0.032
0.1
0.32
1
3.2
10
32
100
(DRUG'S ANTIVIRAL EFFECT)
(DRUG'S CYTOTOXIC EFFECT)

FIGURE 21

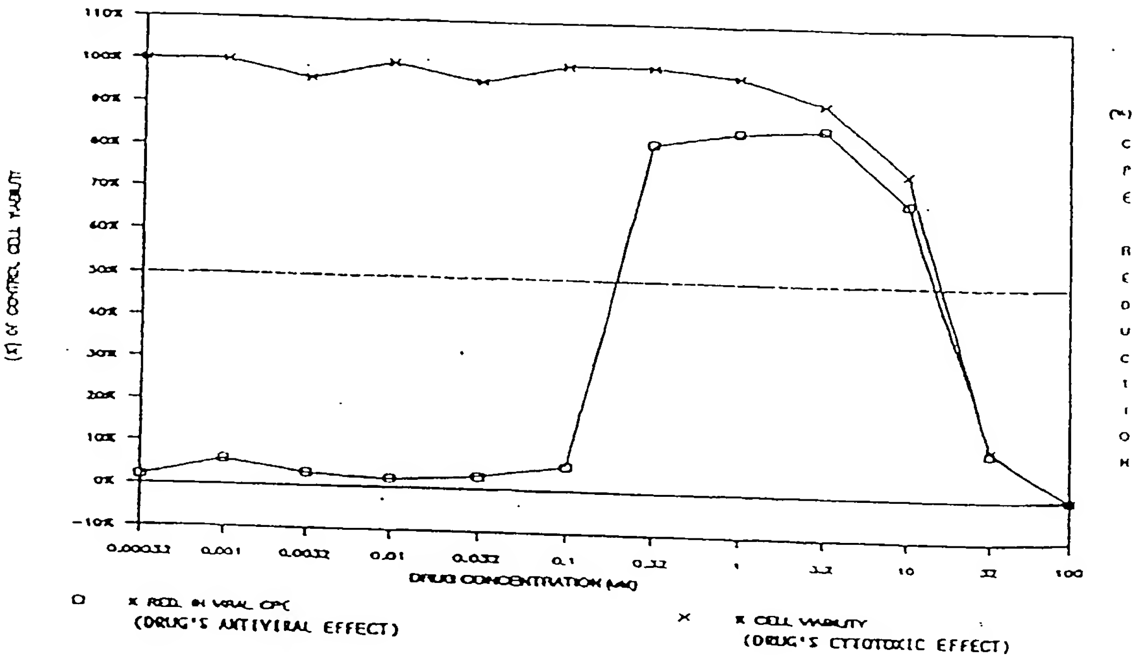


FIGURE 22

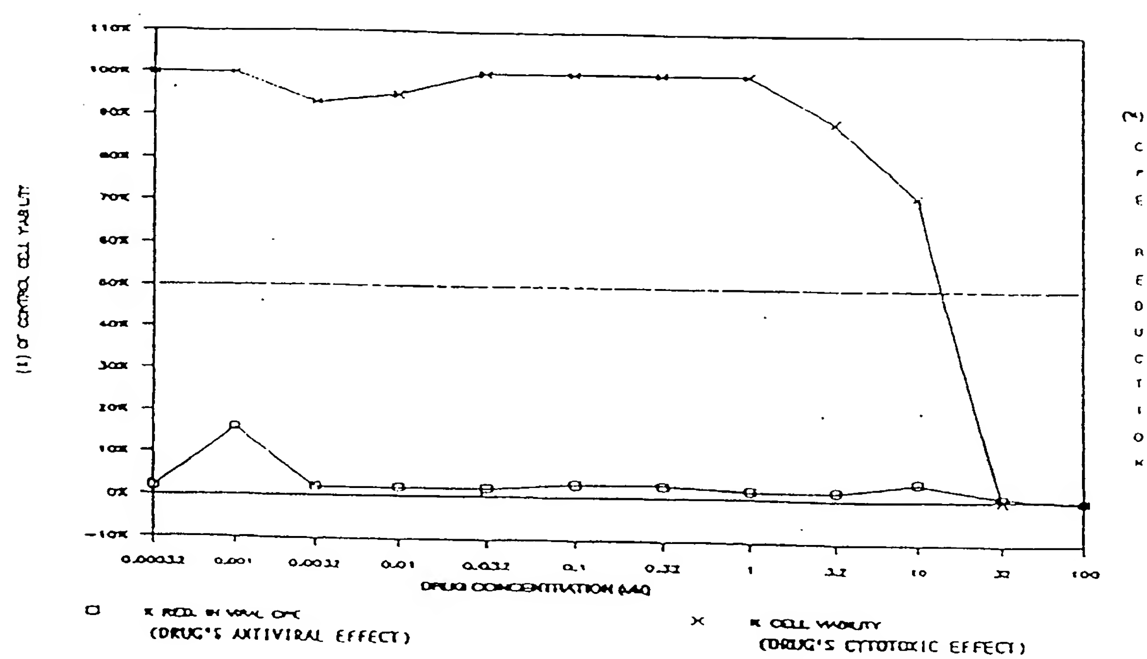

0%
-10%
0.01
0.1
1
10
100
(DRUG'S ANTIVIRAL EFFECT)
(DRUG'S CYTOTOXIC EFFECT)

FIGURE 23

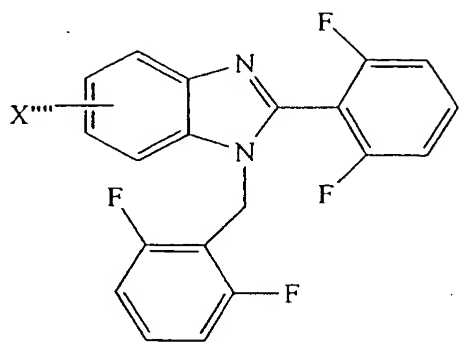


FIGURE 24

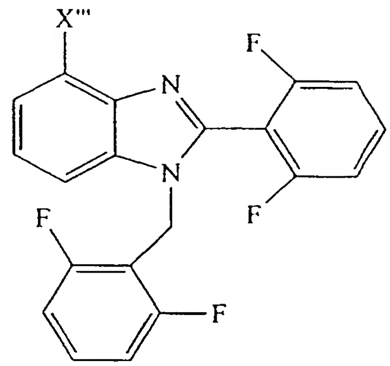
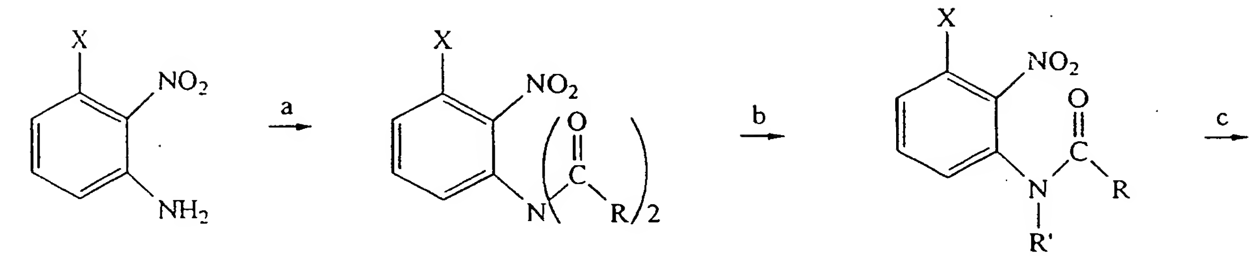


FIGURE 25

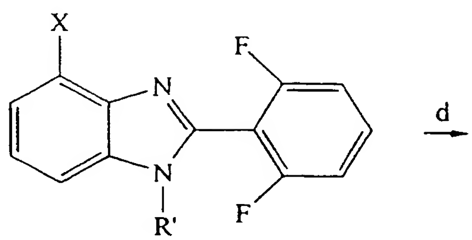
No	formula	calculated C	calculated H	calculated N	found C	found H	found N
26	$C_{20}H_{12}F_4N_2$	67.42	3.39	7.86	67.28	3.44	7.76
28	$C_{20}H_{14}F_2N_2$ x 1/8H_2O	74.47	4.45	8.68	74.43	4.45	8.63
29	$C_{21}H_{16}F_2N_2$ x 1/4H_2O	74.43	4.91	8.27	74.81	4.90	7.85
30	$C_{21}H_{14}Cl_2F_2N_2$ x 1/4H_2O	61.86	3.58	6.87	61.64	3.65	6.80
32	$C_{22}H_{16}F_4N_2O$ x 1/2H_2O	64.55	4.19	6.84	64.63	4.11	6.72
33	$C_{21}H_{14}F_4N_2$	68.11	3.81	7.56	68.17	3.90	7.54
34	$C_{18}H_{18}F_2N_2$	71.98	6.04	9.33	72.06	6.05	9.25
35	$C_{15}H_{12}F_2N_2$	69.76	4.68	10.85	69.56	4.77	10.79
36	$C_{21}H_{16}F_2N_2$	75.44	4.82	8.38	75.16	4.89	8.29
37	$C_{25}H_{18}F_2N_2$	78.11	4.72	7.29	78.00	4.75	7.19
38	$C_{25}H_{18}F_2N_2$	78.11	4.72	7.29	77.84	4.83	7.23
39	$C_{20}H_{14}F_2N_2$ x 1/4H_2O	73.95	4.50	8.62	73.87	4.50	8.60
40	$C_{20}H_{15}F_2N_3$	71.63	4.51	12.53	71.74	4.55	12.62
41	$C_{20}H_{15}F_2N_3$	71.63	4.51	12.53	71.72	4.55	12.58
42	$C_{21}H_{11}F_7N_2$	59.44	2.61	6.60	59.35	2.65	6.50
43	$C_{20}H_{15}F_2N_3$ x 1/2H_2O	69.76	4.68	12.20	69.59	4.38	12.29
45	$C_{19}H_{12}F_2N_2SO_2$	61.62	3.27	7.56	61.68	3.34	7.60
46	$C_{20}H_{14}F_2N_2SO_2$	62.49	3.67	7.29	62.50	3.71	7.24
47	$C_{20}H_{10}F_4N_2O$	64.87	2.72	7.56	64.88	2.77	7.46
48	$C_{16}H_{14}F_2N_2O$	66.66	4.89	9.72	66.74	4.94	9.71
49	$C_{15}H_{12}F_2N_2$ x 1/4H_2O	68.56	4.79	10.66	68.52	4.60	10.7
50	$C_{16}H_{12}F_2N_2O$ x 1/5H_2O	66.29	4.31	9.66	66.57	4.28	9.67

No.	formula	calculated C	calculated H	calculated N	found C	found H	found N
3100	$C_{20}H_{13}F_4N_3$	64.69	3.53	11.32	64.63	3.54	11.20
3400	$C_{22}H_{15}F_4N_3O$	63.92	3.66	10.17	63.94	3.62	10.10
3500	$C_{22}H_{17}F_4N_3$	66.16	4.29	10.52	66.24	4.24	10.47
3200	$C_{20}H_{11}BrF_4N_2$ x 1/4H_2O	54.63	2.64	6.37	54.59	2.47	6.38
1800	$C_{20}H_{11}BrF_4N_2$ x 3/4H_2O	53.53	2.81	6.24	53.23	2.49	6.10
3300	$C_{20}H_{11}ClF_4N_2$	61.47	2.84	7.17	61.59	2.86	7.23
2000	$C_{20}H_{11}ClF_4N_2$	61.47	2.84	7.17	61.37	2.90	7.15
2100	$C_{20}H_{11}ClF_4N_2$	61.47	2.84	7.17	61.31	2.92	7.04
2200	$C_{21}H_{14}F_4N_2$	68.11	3.81	7.56	68.22	3.90	7.60
2300	$C_{21}H_{14}F_4N_2$	68.11	3.81	7.56	67.94	3.86	7.50
2400	$C_{21}H_{14}F_4N_2$	68.11	3.81	7.56	68.02	3.89	7.49
2800	$C_{22}H_{16}F_4N_2$	68.75	4.20	7.29	68.68	4.15	7.28
2900	$C_{20}H_{11}F_4N_3O_2$	59.86	2.76	10.47	59.96	2.78	10.55
3000	$C_{20}H_{11}F_4N_3O_2$	59.86	2.76	10.47	60.24	2.89	10.38

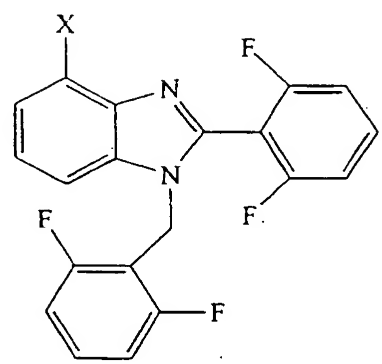
FIGURE 26



4001 X = CO_2CH_3 **4002** X = CO_2CH_3, R = 2,6-F_2Ph **4003** X = CO_2CH_3, R = 2,6-F_2Ph, R' = H



4004 X = CO_2CH_3, R' = H



4005 X = CO_2CH_3

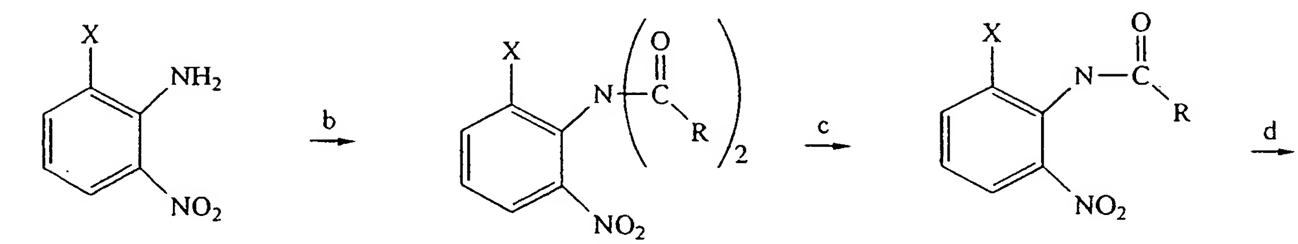
e

4006 X = CO_2H

f

4007 X = CN

FIGURE 27

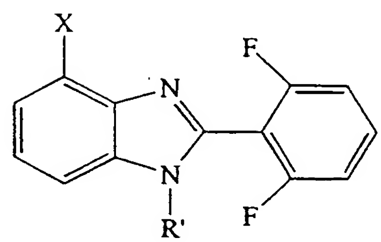


5001 X = OH

5002 X = OCH_3

5003 X = OCH_3, R = 2,6-F_2Ph

5004 X = OCH_3, R = 2,6-F_2Ph



5005 X = OCH_3, R' = H

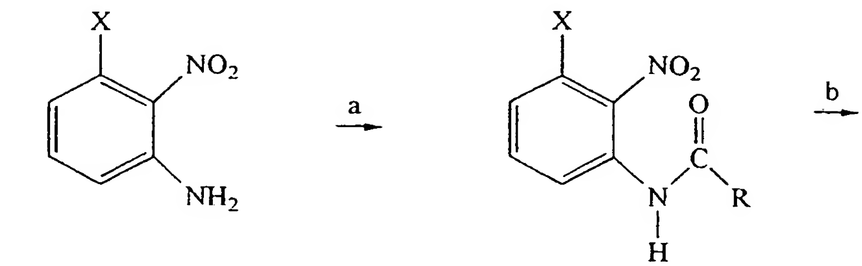
5006 X = OCH_3, R' = 2,6-F_2Bn

5007 X = OCH_3, R' = Bn

5008 X = OCH_3, R' = $BnCH_2$

5009 X = OCH_3, R' = CH_2-CH=C$(CH_3)_2$

FIGURE 28

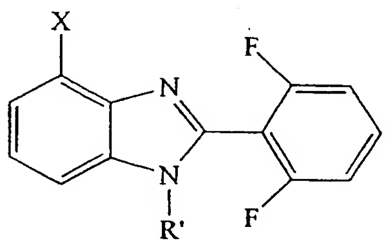


4008 X = CH_2CH_3

9 X = CH_3

4009 X = CH_2CH_3, R = 2,6-F_2Ph

6001 X = CH_3, R = 2,6-F_2Ph



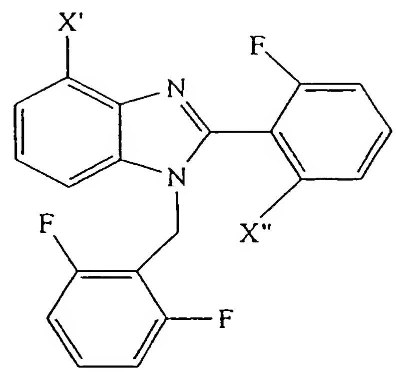
4010 X = CH_2CH_3, R' = H

4011 X = CH_2CH_3, R' = 2,6-F_2Bn c

6002 X = CH_3, R' = H

6003 X = CH_3, R' = CH_2-CH=C$(CH_3)_2$ d

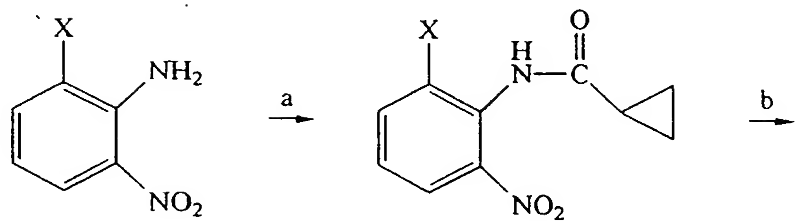
FIGURE 29



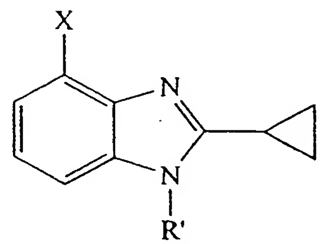
5008 X' = NO_2, X" = OCH_3 → (a) 5009 X' = NH_2, X" = OCH_3

5010 X' = HNAc, X" = F → (b) 5011 X' = MeNAc, X" = F → (c) 5012 X' = MeNH, X" = F

FIGURE 30



5002 X = OCH_3 5013 X = OCH_3



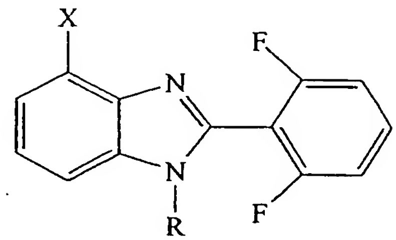
5014 X = OCH_3, R' = H

5015 X = OCH_3, R' = CH_2-CH=C$(CH_3)_2$

5016 X = OCH_3, R' = 2,6-F_2Bn

c d

FIGURE 31



4012 X = NO_2, R = H

a

4013 X = NO_2, R = CH_2-CH=C$(CH_3)_2$

b

4014 X = NH_2, R = CH_2-CH=C$(CH_3)_2$

4015 X = C(OH)$(CH_3)_2$, R = 2,6-F_2Bn

c

4016 X = isopropenyl, R = 2,6-F_2Bn

FIGURE 32

Cross Resistance Profile of 4-Substituted 1-(2,6-difluorobenzyl)-2-(2,6-difluorophenyl)benzimidazoles in Cytopathic Cell Killing Assay

Isolate	(X= CH_3) R= 2,6-F,Bn	(X= H) R= 2,6-F,Bn	(X= CH_3) R = prenyl	TIBO	nevir.	TZB
NL4-3	0.5	2.2	1.3	0.3	0.04	1.0
L74V	0.3	1.9		0.2	0.04	0.8
A98G	2.7	4.7		1.1	0.8	10
L100I	0.3	1.3	0.3	>10	0.2	6.6
K101E	>10	>20	>20	>10	1.1	>10
K103N	>20	>10	>20	>10	>10	>20
V106A	>10	>20		>10	>10	>10
V108I	2.8	>10	>20	2.4	0.4	5.7
V179D	0.7	2.9		6.2	0.2	3.9
Y181C	4.3	14	>20	4.2	4.9	>10
Y188C	3.0	>10		>20	>0.5	>20
4XAZT	0.1	0.3		0.3	>0.5	1.1
4XAZT /L100I	0.2	0.9		>20	0.1	1.1
4XAZT /Y181C	3.5	>20		2	3.0	>10

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/03588

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D235/18 A61K31/415 C07D235/08 C07D235/06 C07D235/12
C07D401/04 C07D401/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 471 991 A (MONFORTE PIETRO ;MONFORTE ANNA MARIA (IT); ZAPPALA MARIA (IT); ROM) 26 February 1992 see claims ---	1,4,9-18
A	ALBA CHIMIRI ET AL: "Anti -HIV agents II.Synthesis and in vitro anti-HIV activity of novel 1H,3H-thiazolo'3,4-a!benzimidazoles" IL FARMACO., vol. 46, no. 7,8, 1991, PAVIA IT, pages 925-933, XP002066965 see the whole document ---	1,4,9-18
A	FR 2 092 648 A (FUVEAU SA) 28 January 1972 see the whole document ---	1,9-18

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
4 June 1998	22.06.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	THOMAS ROTH ET AL: "Synthesis and biological activity of novel nonnucleoside inhibitors of HIV-1 reverse transcriptase.2-aryl-substituted benzimidazoles" JOURNAL OF MEDICINAL CHEMISTRY., vol. 40, no. 26, 19 December 1997, WASHINGTON US, pages 4199-4207, XP002066966 see the whole document -----	1-18

1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 98/03588

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9-18
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte .onal Application No
PCT/US 98/03588

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0471991	A	26-02-1992	IT	1243362 B	10-06-1994
			CA	2047796 A	26-01-1992
			JP	4234395 A	24-08-1992
			US	5217984 A	08-06-1993
FR 2092648	A	28-01-1972	NONE		